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A REVIEW OF VISCEROPTOSIS AND ALLIED ABDOMINAL CONDITIONS ASSOCIATED WITH CHRONIC INVALIDISM

PART II

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Harris and Chapman (264) in 551 cases found that 78 showed free HCl between 20–30, 56 below 20, 247 above 30, and 23 achylia. These figures are roughly the same proportionate variations to be found in a similar group of healthy individuals. Campbell and Conybeare (106) found high acidity with a high-placed hypertonic and rapidly emptying stomach, the most common association. On the other hand, low acidity with a low, hypotonic, slowly emptying stomach was found less constantly associated.

Keeton (338), experimenting with a Rehfuss tube, found that when it reached the duodenum in a visceroptotic patient nausea was produced, accompanied by dizziness, sensations of pressure in the head and neck, headache, and syncope. He suggests that nausea results from a motor duodenal dysfunction, probably antiperistalsis. The other sensations he regards as evidence of a low threshold of sensibility, which allows stimuli from the duodenum to reach the central nervous system through the autonomic nerves, and there overflow into the vasomotor centre.

Other observers consider that all the symptoms arise from a disturbance in the vasomotor system and that the alimentary tract is affected only secondarily. Larimore (389), using Mill's classification, studied the blood-pressure in relation to types of body habitus in 417 factory workers. He found the sthenic habitus shows a higher blood-pressure than the asthenic, while the pressure in the hyposthenic group was intermediate. The average blood-pressures were approximately the same for male and female asthenics (males 106/63, females 105/68). Hyposthenics are also approximately the same (males 116/71, females 115/72). The sthenic group showed somewhat higher pressures for males (males 126/78, females 118/73).

These relations did not change when types were separated into groups of age decades. Robertson (520) thought that the symptoms can be explained by disturbances in the abdominal circulation. Mallory (415) agrees with him, pointing out that there is a relative vasomotor paresis in these individuals,

evidenced by a fall in blood-pressure and rise in pulse-rate when they pass from the recumbent to the erect posture. This determines an engorgement of the abdominal viscera, which, increasing in weight, drag on the mesentery. This in turn leads to further disturbances of vasomotor control and motor dysfunction, with pocketing of gas in the intestinal loops resulting in sensations of fullness and tension. Mallory thinks that the reason why enemata and cathartics produce temporary relief is because they deplete the splanchnic circulation. Fossier (208), on the other hand, regards the elongated narrow ascending aorta, attenuated aortic semicircle, and the drop heart found in asthenics the chief cause of their troubles. He attempts to show, by the principles of mechanics, that blood flowing through a narrow arch and elongated ascending aorta will loose 10–30 mm. of pressure, and the consequent low blood-pressure constantly present is the factor productive of symptoms. The mechanical principles he invokes apply, however, only to rigid tubes, and not to living muscular structures like the aorta.

Netschajew (482) claimed to find non-striped muscle-fibres in the mesentery and peritoneal ligaments. These are innervated by the sympathetic, and relaxation of their tone allows the viscera to drop. For him it is the mental state of the individual which brings about the low position of the viscera and produces the symptoms and not vice versa.

Hurry and Fenwick (292), on the other hand, return to the pre-radiological theories and regard visceroptosis as a 'vicious circle' disease belonging to the group which includes pulmonary tuberculosis, cardiac failure, obesity, neurasthenia, and chronic constipation *inter alia*!

Autointoxication and Constipation.

'On the periodic functioning of the colon,' says Lord Dawson (161), 'depend our health, comfort, mental alertness, and emotional outlook to a greater degree than we care to confess.'

Mankind seems to be strongly prejudiced against such an assumption, and from the very earliest times preferred a quite different explanation of the mental and physical discomforts so frequently associated with irregular bowel movements. With a remarkable uniformity from one period to another has persisted the belief that absorption of toxic substances must of necessity accompany constipation. There are few pathological conditions which have not at one time or other been attributed to it. Judged by later standards Von Haller (262) erred on the side of moderation when he stated that fever, consumption, haemorrhage, and insanity are the inheritance of constipation. In 1805 James Hamilton published his 'Observations on the Utility and Administration of Purgative Medicines' in diseases as diverse as typhus fever, marasmus, chorea, and haematemesis. Twenty years later the publication of Esquirol's (191) observations on the intestinal displacements in maniacs gave rise to a school of copropsychiatry which had its day and passed away until its revival at the beginning

of the present century. In this age of scientific medicine we still find a great number of morbid states attributed to poisons of gastro-intestinal origin. These include not only such minor conditions as headache, malaise, lassitude, &c., but also sciatica, tetany, epilepsy, eclampsia, many forms of dermatitis, various forms of nervous disease, myxoedema and cretinism, chlorosis, and pernicious anaemia, cirrhoses, nephritis, arteriosclerosis, and cancer!

The belief that a displaced intestine worked at a mechanical disadvantage and was inefficient in passing on its contents was not unreasonable in the light of the knowledge available before the birth of radiology. But the persistence of the idea that poisonous substances were formed in the intestine and absorbed into the body from there, despite repeated failure to demonstrate their existence, suggests an emotional, rather than a scientific, state of mind. Long before investigators attempted the isolation of this toxic substance theories were elaborated to explain how and where it was formed. James Jackson (318) over a hundred years ago suggested it originated in the putrefaction of animal food and in the acetous fermentation of vegetable food. In the middle of the century Senator (552) revived the idea that protein decomposition of any sort might originate the toxin. But it was left to Bouchard (78) in 1887 to beguile thought by the ‘false imposture and force of words’ with the term autointoxication. This word has survived in the phrase of Albutt (8), ‘to oppress and mislead us, as other ghosts do, when the underlying thing has dissolved’. For it is to be remembered that Bouchard regarded the stomach as the site of absorption of the poison, and not the colon. He makes it quite clear that autointoxication results from a congenital weakness of the muscle fibres of the stomach, which allows it to dilate. The contents, no longer completely evacuated, stagnate and decompose, and from this decomposing mass are absorbed poisonous substances. On the other hand Mathieu (423) and his co-workers showed that where there was true obstruction and stagnation, and where putrefying contents could be withdrawn by the stomach tube, as in cancer of the pylorus, there were no symptoms of autointoxication present. Yet in cases of autointoxication the stomach tube failed to reveal any putrefying contents in the stomach.

The word ‘autointoxication’ then became applied to poisoning from the bowel, the result of chronic constipation, and thereupon began the search for the hypothetical toxin and the elucidation of its relationship to numerous general disorders presumed to be caused by it. Weintraud in Ergeb. allg. Pathol. (4) of 1897 exhaustively reviewed the work done up to that time and found the evidence for the existence of such a toxin non-proven. With the opening of the present century the idea, through the work of the surgeons, again came to the front, and received great impetus from Metchnikoff (443–5). This worker, with much skill and eloquence, attempted to prove that most of the manifestations of senility come from putrefaction in the large bowel, and suggested that the colon was a useless structure which man was better without. Combe (139) proposed a modified Bouchard theory to the effect that a diet too rich in protein in a stomach showing motor insufficiency tended to ferment. This fermenting

material on reaching the intestine produces there a spasm, and this spasm leads to stasis and further decomposition.

To Herter (275) belongs the credit of first investigating the subject on really scientific lines according to the type of pathogenic organism at work in the intestine. He proposed a classification of cases of autointoxication into: (1) An indolic type, characterized by indicanuria, originating from the putrefaction of protein by members of the *B. coli* group of organisms. (2) A saccharo-butyric type, characterized by the absence of indicanuria, originating from the fermentation of carbohydrates by anaerobes. (3) A mixed type, a combination of (1) and (2). However, the bacteriological evidence he brought forward in support of his views failed to carry conviction.

As more and more of the possible products of gastro-intestinal putrefaction became known, isolated, and experimented with, each in turn failed to produce the symptoms of autointoxication. This failure led Adami (4) to put forward his sub-infection theory, that the cause was not a chemical absorption but a bacteria invasion of a body of a special kind. He assumed that intestinal organisms were continually passing through the intestinal mucous membrane in numbers sufficient to pass the barrier of lymphatic glands, but not sufficient to retain a foothold in the tissues of the various organs they eventually reached and where they were destroyed. This continuous destruction led to the tissues wearing out and a true acute or chronic infection supervening. Satterlee (537–8) appears to be the only supporter of this view. He finds that all the colons he has removed show signs of infection of the lymphatic vessels and glands in the mesentery. From these he claims to have isolated *B. coli* and streptococci at operation. He holds that these patients suffer from a toxaemia from the toxins elaborated in these lymphatic glands and that it is only later, when the defensive barrier breaks down, that a true bacteriaemia occurs. Lane's school, on the other hand, holds the primary condition to be a chemical toxaemia which, by lowering the resistance of the intestinal mucosa, only later permits an invasion of the body by micro-organisms. Mutch (478), recognizing that none of the hitherto isolated putrefactive substances in the bowel had been proved to be toxic, attempted to solve the problem. Admitting that the large bowel is delegated to the bacterial destruction of food residues, he considered that the flora engaged in this destruction works in relays. The intermediate products which are toxic are seized upon in normal circumstances by successive strains of organism, until the final innocuous bodies are formed. In intestinal stasis this relay race is interfered with so that the final innocuous substance is never reached. Instead, the process stops short at beta-iminazo, a depressor substance derived from histidin. It is the presence of this substance in the blood which produces the symptoms of autointoxication. Mellanby (442), however, found that beta-imanazo could be obtained only with a pure culture of a certain strain, and that in the presence of other organisms, as in the bowel, it was rendered inert as rapidly as it was formed. Wells (621), after an extensive review, finds that few of the known products of gastro-intestinal putrefac-

tion are toxic to any considerable degree. Those that might be toxic are probably produced in too small quantities to cause any appreciable effect, especially in view of the detoxicating and eliminating powers of the intestines, liver, kidney, and other organs. Alvarez (16) also shows how inconclusive is all the evidence so far submitted to prove that substances absorbed from the alimentary canal are common or important sources of intoxication.

Since the publication of Alvarez's paper, Power and Sherwin (503) have produced further evidence against the existence of a putrefactive toxin. They found that 50 mg. of skatol or indol might be ingested daily without producing more than nausea, loss of appetite, headache, melancholia, and sleeplessness. They find that from the chemical standpoint putrefactive products belong to two classes, those containing nitrogen and those not. The nitrogen containers are formed by the action of certain bacteria which remove CO_2 from the acid group of the protein derivative and belong to the amines. In the non-nitrogen containers the nitrogen is first removed and the compound which remains is acidic in character, and contains only carbon, hydrogen, and oxygen. They prepared chemically pure samples of all known amines and of the non-nitrogenous products. Although amines are 20-100 times more toxic than the non-nitrogenous compounds, neither produced any of the classical symptoms when ingested by individuals in doses of 1 gm. in twenty-four hours. The amines produced nausea, loss of appetite, high nervous tension, sleeplessness, feelings of impending evil, and always a severe diarrhoea, with a slight rise in temperature, pulse-rate, and blood-pressure. The non-nitrogenous products increased appetite, slowed the cerebral functions and produced drowsiness. The difference in toxicity appeared to depend chiefly on rapidity of absorption and the length of time necessary for detoxication. Their experiments showed that the human body is equipped with a chemical defence mechanism that is capable of detoxicating the various types of putrefactive products formed within the intestines, and at the same time is able to cope with larger quantities of these products than are normally present within the intestine. They conclude by saying that this chemical defence mechanism is non-specific in character and more than adequate for the detoxication of the small amounts of putrefactive products normally produced in the human intestine by the action of a putrefactive bacteria on unabsorbed protein material. That this defence mechanism is widespread in the body is made clear by numerous experiments.

G. H. Whipple, in a series of papers beginning with that on Proteose Intoxication (*J.A.M.A. 1916*, lxvii, 15), showed that the highly toxic substances formed in an obstructed loop of small intestine are harmless when put into a healthy intestine.

Koessler and Hanke (357) found that 500 mg. of histamine produced no effects whatever when placed in a dog's intestinal tract, and that less could be recovered than had been put in, showing that some had been destroyed by the intestinal mucosa.

In the case of toxic substances which are absorbed, Richards and Howland

(621) confirmed Herter and Warkeman's (277) work that the liver is capable of conjugating indol and similar substances into harmless compounds. Finally, that this detoxicating property is not specific for the liver cells was demonstrated by Koessler and Hanke (357), who injected histamine into the portal vein, femoral artery, and femoral vein of dogs. The dose injected into the portal vein and the femoral artery was equally detoxicated, whereas that injected into the femoral vein produced toxic symptoms. This suggests that the detoxicating action resides in the capillary bed and is probably a function of the reticulo-endothelial tissue in general. Jordan, Kellog, and others held that the symptoms of autointoxication only arise when colonic stasis produces an incompetence of the ileo-caecal valve permitting invasion of the sterile lower ileum by bacteria. Andrews (23) showed, however, that whereas the duodenal contents in health contain few organisms, yet bacterial multiplication recommences before the terminal ileum is reached. This is not surprising in view of the readiness with which members of the coli group and the more resistant streptococci grow in bile. Macleod (410) states that in the small intestine in man there are present normally bacteria capable of acting on carbohydrates. These produce lactic, acetic, and other acids which inhibit the action of any protein digesting bacteria present. Probably there are also present bacteria capable of splitting fatty acids into glycerine. In the large intestine cellulose and protein digesting bacteria predominate. It was on the predominance of one or other of these two groups of bacteria in the stools that Herter and his school based their diagnosis of intestinal intoxication, but this claim was never substantiated for adults. In children Porter, Morris, and Meyer (499) claimed to be able to identify a putrefactive, a fermentative, and a normal stool by bacteriological examination. Davison and Rosenthal (160), however, showed that the so-called putrefactive and fermentative stools occur almost as frequently in normal children as do normal stools. They found that the organisms said to be those of putrefaction were harmless saprophytes.

In children with symptoms, a fermentative stool does not indicate that organisms of fermentation are producing the symptoms. All the evidence is in favour of the view that the symptoms are due to the small intestine being unable to absorb carbohydrate which, being passed on to the colon unchanged, is there fermented by *B coli* group. On the other hand, where there is delayed absorption of protein the same organisms putrefy the unabsorbed portion into the amines. Tissier (589), basing his work on the earlier observations of Senator (553) and Escherich (190), demonstrated that the intestinal flora of infants is constant in composition according to the food. In breast-fed infants *B. bifidus* is the predominating organism, and in the bottle-fed infants *B. acidophilus*, but as soon as the child is taking a mixed diet the intestinal flora assumes the adult type with *B. coli* predominating. Metchnikoff hoped that by sour milk feeding the *B. coli* might be inhibited by the growth of *B. acid lacticus* and the colon thereby purified, but this hope remained unfulfilled. Herter and Kendall (276) continued Tissier's work, and found in adults a definite correlation to exist

between specific types of bacteria and the chemical composition of the ingested food. They concluded that the intestinal flora is fundamentally a physiological unit rather than a heterogeneous collection of adventitious micro-organisms. Then Rettger and Cheplin (513–4) introduced the *B. acidophilus* which, under experimental conditions, succeeded in maintaining a foothold in the intestine but died out in a few days after the resumption of ordinary diet. It was hoped that the administration of lactose would enable the *B. acidophilus* to survive. However, Dragstedt, Cannon, and Dragstedt (170) have shown that any delay in the passage of the intestinal contents results in a proteolytic flora irrespective of the character of the diet. In conditions of delay even such carbohydrates as dextrose and lactose are probably completely absorbed in the upper part of the intestine, and so cannot reach the colon to liberate there sufficient acid to inhibit proteolytic organisms. Normally they do this because, not being easily absorbed, they reach a part of the intestine where bacterial growth is at a maximum.

Dudgeon (177), in a very valuable article, has shown that spirochaetes, streptococci, long and short chained and haemolytic, haemolytic colon bacilli, staplylococci, *aureus*, and *albus*, diphtheroids, and anaerobes like *B. Welchii*, may all be isolated from the faeces of healthy individuals. He confirms the work of previous investigators who found that the number of micro-organisms in the intestinal canal depends, in health, largely upon the number introduced by the mouth. He finds that among the normal population who have committed dietetic errors bacteria foreign to the faeces may be found, and also that the common inhabitants, the enterococci and non-haemolytic colon bacilli may be greatly increased in number. Bacteria, haemolytic colon bacilli, for example, which are present in the faeces in a small proportion of normal individuals, but then only sparsely, may as a result of an intestinal disorder appear in greatly increased numbers. On the other hand, a true pathological process affecting the colon may not produce a greater or more varied bacterial flora than may occur among healthy subjects whose diet has been at fault. In a more recent article (178) he concludes thus: ' Much time will be saved, and endless discussion, if it is realized at the outset that the presence of an organism in the faeces is not an indication of an intestinal infection with that organism. Unfortunately the term 'intestinal infection' has been so loosely employed, and so 'readily proved' that it is without significance to those who have studied the bacteriology of the intestinal tract in man.'

Cotton, a most enthusiastic exponent of the colon as a source of systematic disease, appears to lean towards the sub-infection theory (142–5). Not holding with the hereditary and psychogenic causation of mental disorder he believes that all functional psychotics owe their disabilities to foci of infection in teeth, tonsils, and colons. Draper (174–5) finds 20 per cent. of the colons he removes for Cotton show gross pathological changes. However, Ewing (145), reporting on the histological appearances of these colons, failed to find any change which indicates that bacteria have invaded their walls, blood-vessels, or lymphatics. Even in the absence of such findings he remains of the opinion that the damage

to the epithelial structure is likely to be followed by untoward consequences. Warren and Whipple (614), by suitable doses of the X-rays, destroyed the intestinal epithelium, leaving empty crypts and naked villi exposed to swarms of bacteria in the bowel. Notwithstanding, there was no invasion of the tissues, lymph, or blood by the alimentary micro-organisms found in the masses of exudate. This suggests that the intestinal epithelium is not the all-important barrier that protects the tissues from invasion, and it is probable that other tissues or tissue juices have a protective mechanism which is of much importance and not to be neglected in estimating the resistance of the intestine to bacterial invasion. Finally, Cotton's technique for the discovery of focal infection has been adversely criticized by most bacteriologists (358). On the clinical side Kopeloff and Kirby (359), in a series of 120 cases of manic depressives, praecox cases, psychoneurotics, and psychopathic personalities, found that the removal of all definite foci of infection in 58 did not bring about a higher percentage recovery rate than in a comparable 62, in which foci were not removed. In every case which recovered, recovery had been forecasted before treatment was instituted, and no case recovered in which a poor prognosis had been given irrespective of the treatment adopted.

It has been admitted by certain supporters of the toxaemia theory that the behaviour of the individual towards the hypothetical toxin is just as important as the action of the toxin on the individual.

Thus we find Herter (275) writing 'We must content ourselves with the suspicion that chronic toxication through the absorption of similar quantities of the same poisonous material produces different effects in different persons. That the mental and emotional peculiarities of individuals have a large part in fixing the type of nervous reaction has become apparent to careful students of pathological conditions.'

More significant still is Monod's (458) statement that the toxins circulating in the blood of a patient A, and causing great disturbance, might, if run into the system of a patient B, do no harm whatsoever, thus showing that the soil is as important as the seed. That the soil is a very important matter has been conclusively demonstrated for an allied condition, and one which bears a much closer resemblance to a toxaemia of intestinal origin than does intestinal stasis. I refer to the acute food disorders of infancy. The persistent diarrhoea and vomiting, resisting in severe cases all forms of medication, and continuing until dehydration and collapse bring about a fatal termination, appear to present a perfect picture of bacterial or chemical poisoning. Yet the most assiduous research has failed to isolate a pathognomonic organism or a specific toxin, and post-mortem examination has equally failed to show any characteristic patho- logical appearance. It was not until Finkelstein (200) published his observa- tions that any light was thrown upon this mysterious though common disorder.

He found that disturbances of nutrition in infancy could be divided into four types, and that these types represented the chief varieties of reaction of the child's system to the food given. Their severity depended on two factors, the

degree of unsuitability of the food, and the extent of the functional debility of the infant. He observed that a food which appears to suit a perfectly healthy child, or at any rate produces no harm, very often sets up serious illness in a weakly infant.

For health it is necessary that the structure of the body and the function of nutrition should both be normal; otherwise the child cannot assimilate a diet which may be quite suitable for a healthy one. The truth of his observations will be found in the success which has followed their application to infant feeding. Strangely enough, the possibility that this congenital enfeeblement of the function of nutrition might persist into adult life has been little stressed by recent workers. General opinion seems to suggest that if a *diet* be scientifically constructed, it is then a suitable *one* for all individuals, and conversely, that disorders of nutrition are entirely the result of a faulty diet. The fault is, according to McCollum (436), McCarrison (433), and others, often a compound of deficiency in association with excess.

Taking a diet, not uncommon among the poorer classes, of white bread, margarine, condensed milk and tea, a minimum of imported meat and boiled potatoes, McCarrison holds that such does not contain a sufficiency of vitamins to activate the cells of the digestive system to healthy function. Its richness in starch favours an increase in fermentative organisms, and makes relatively more deficient the vitamin necessary for healthy cellular activity. It does not contain sufficiency of salts to provide the proper medium for the chemical processes of digestion, nor does it contain a sufficiency of vegetable residue or cellulose to ensure a normal action of the bowel. Cramer (150-1) has produced experimental evidence to show that the functional integrity of the digestive tract is dependent on the presence in the food of certain substances with specific drug-like action very much in the same way as the functional integrity of the uterus is dependent on a hormone produced by the ovary. He found that fat-soluble vitamin A has a specific stimulating effect on the intestinal mucous membrane which atrophies in its absence; and that water-soluble B has a stimulating effect on lymphoid tissue, on the processes of digestion, and on absorption from the intestinal canal. He observed that the first effect of vitamin A deprivation closely resembles what occurs in X-ray intoxication as demonstrated by Mottram (471), namely, an increase in the mucin-secreting cells and an increase in mucin production going on to exhaustion.

Finally, the cells atrophy and bacteria penetrate into the crypts left. In a healthy intestine Cramer states that the bacterial and protozoal flora are confined to the centre of the lumen probably, as Bond (75) thinks, because due to the biochemical action of the mucin at the periphery. With the disappearance of mucin, the bacteria reach the intestinal walls and, in the presence of a vitamin B deficiency, invasion of the mucosa occurs with the production of a toxaemia.

Murlin (476), however, experimenting with vitamin B, finds that constipation which results from its deficiency is due to retention of faeces in the large intestine, and that the passage through the small intestine is normal. Wells (621)

shows there is good evidence for regarding vitamin A as consisting of two separate factors—a growth factor and an anti-neuritic factor—and vitamin B as consisting also of a growth factor as well as its anti-neuritic factor. Cogwill (147) found that absence of vitamin B in addition to the production of neuritis resulted in a decreased desire for food and inability to utilize it, and in this was confirmed by Findlay (199) and Werkman (622).

This is explained by Farmer and Redenhaugh (196) by the assumption that vitamin B is a precursor of certain alimentary enzymes. Cowgill, Plummer, &c. (148), find that in severe degrees of vitamin B deficiency there is anorexia, nervous and muscular symptoms, and gastric atony. They suggest that a certain proportion of vitamin B is essential for normal gastric tonicity. However true these findings may be for laboratory animals, there is very little evidence that the existing vague ill-health in the general population depends on vitamin starvation.

Hutchinson (308) states that he has never seen amidst the London Hospital out-patients any evidence that minor degrees of vitamin starvation are common among the general population. Moreover, Helen Mackay (408) points out that vitamin B has such a widespread distribution and such a resistance to heat and storage that anything like deprivation in general is impossible.

Strangely enough McCarrison's experimental findings confirm the view that certain individuals inherit a tolerance for grave departures from the normal in nutrition. He found that of a hundred pigeons exposed under precisely similar conditions to vitamin starvation 25 per cent. flourished, 50 per cent. remained at maintenance level, while 25 per cent. went steadily downhill. This can only mean that certain pigeons withstand the most gross disturbances in nutrition without being much affected, thereby depending upon their inherent resisting power.

On the clinical side Barnett (97) has shown that individuals may inherit an inability to handle a normal balanced diet. For him malabsorption is at the root of many of the disorders attributed to vitamin deficiency. In these cases the food ingested may be insufficient to supply the demands of the body and leave at the same time a residue sufficient to stimulate excretion ; or sufficient food is consumed, but on account of it being incomplete or faulty it passes too rapidly through the digestive tract. He brings evidence to show that a food may be theoretically correctly balanced, and yet faulty for certain individuals who can only find intestinal health by adjusting their ways of eating to their own complex and delicately-adjusted digestive apparatus (95).

Bryant (85) and Alvarez (19) have brought evidence to show that the chronic intestinal invalid can be considerably helped, provided the diet is fitted to the individual and not the individual made to fit the diet. In the majority of cases as soon as a suitable diet is found for the patient the signs of 'toxaemia' clear up, irrespective of the diet being an ideal one or not. From this brief review it will be seen that there is no evidence that the intestine harbours disease-producing poisons elaborated from the inspissated stool of constipation.

The evidence, not here considered, is all to the contrary, namely, that true intestinal autointoxication is accompanied by diarrhoea and not by constipation. MacNeal, Latzer, and Karr (411) calculated that 46 per cent. of the total faecal nitrogen in the distal two-thirds of the colon is bacterial, and found that in a formed stool the bulk of the bacteria are dead.

Macleod (410) states that on an average diet after twenty-four hours the faeces amounts to 100 grm. This, if retained, diminishes from inspissation to 20 grm., of which 5 grm. are bacteria, mostly dead. In fact, inspissation and the formation of scybala are not the least important safeguards of the intestinal tract against intoxication. Lockart Mummery in *Diseases of the Rectum and Colon* pointed out that all sufferers from constipation are by no means subjects of autointoxication, and, conversely, that many who suffer from autointoxication have neither stasis nor constipation. It is not uncommon, he says, to see a patient who has all the symptoms of intoxication have a daily action of the bowel. He has repeatedly noted the total absence of symptoms in the most extreme cases of colon stasis ; the most alarming symptoms in other cases if faeces were retained for more than twenty-four hours ; and finally, cases which only presented intoxication phenomena when a purgative was administered to relieve their constipation. Hence it is pertinent to enquire : What is constipation, and what is its relation to symptom formation ? The generally-accepted definition of constipation is that of Hurst (301), who defines it as a condition in which none of the residue of a meal taken eight hours after defaecation is excreted within 40 hours. He divided all cases into two great classes—intestinal constipation, in which the passage through the intestines is delayed whilst defaecation is normal, and pelvi-rectal or dyschezia, in which there is no delay in the arrival of the faeces in the pelvic colon, but their final excretion is not performed adequately. As regards the time of passage of the intestinal contents Hurst states that an opaque meal fills the caecum in $4\frac{1}{2}$ hours, the hepatic flexure in $6\frac{1}{2}$ hours, the splenic flexure in 9 hours, the pelvic colon in 12 hours, and the rectum in 18 hours. Jordan (326) gives slightly different figures : caecum $3\frac{1}{2}$ hours, hepatic flexure 5 hours, splenic flexure 8–12 hours, rectum 34 hours ; and by 48 hours all should have been evacuated.

Most radiologists give figures approximating between these two, and most agree that in both stasis and non-stasis the head of the column reaches the different landmarks in approximately these times. Where difference of opinion arises is over the length of time during which the opaque material is retained in different segments of the colon. The two extremes are represented by De Martel and Antoine (417), who state that the caeco-colon should be empty after 15 hours, and by Hurst, who considers 24 hours within the range of normality. These times have not escaped criticism. Burnett (93, 94, 96), for instance, has pointed out that the large amount of barium given with a small test meal acts like agar agar and speeds up the progress of the material through the bowel. By the carmine method he finds that 62-134 hours is the variation of normal intestinal rate in health. Alvarez and Freedlander (20), using small glass beads as

indicators,. found that the rate of progress varies widely in normal healthy persons. They found that scarcely more than half of the ingested beads were passed by the end of the second day. Sometimes days or weeks elapsed before all the beads were recovered from the stools. No symptoms were presented by individuals who required a week or more to pass 70 per cent. of the beads. They believe, along with Burnett, that fast rates—that is, an evacuation of 85 per cent. of the beads in 24 hours—are associated with the passage of soft, badly-digested stools. Kantor (333), assuming 15 hours to represent the normal emptying-time of the caeco-colon, finds this time was exceeded in :

549 of 1229	unselected gastro-intestinal cases or				44·6 per cent.	
129 „	264	asthenics			48·8	„
216 „	437	cases presenting average caeca			49·4	„
10 „	17	„	„	high „	58·8	„
61 „	100	„	„	low „	61·0	„
48 „	62	„	„	redundant colon	77·4	„

In the cases with the highest percentage of constipation, i. e. cases of redundant colon, symptoms of toxaemia were conspicuous by their absence, while in cases of low caeca, especially characterized by the so-called toxaemic symptoms, the incidence of constipation was much less. More striking still was the low percentage of constipation amongst the out-and-out asthenics, confirming the non-relationship of constipation to asthenic symptoms.

According to Alessandrini (7), under physiological conditions two zones exist in which stimulation induces an expulsive peristalsis. One consists of the caecum and ascending colon, the stimulation of which determines the great peristaltic movement of Holzknecht. The other consists of the ampullary portion of the rectum, whose stimulation may provoke reflexly a large expulsive movement, such as may be caused by a glycerine suppository or the very act of defaecation.

Prior to the demonstration of spastic constipation by Fleiner (201), atony had always been considered the fundamental factor in the production of the condition. Lane's operative treatment of chronic constipation was based largely upon this assumption. Even surgeons who did not follow him blindly felt that it was a reasonable procedure to perform a hemicolectomy, and by removing a toneless caeco-colon allow the remainder to function unhampered by the 'cesspool' behind it. Yet Lane, in a communication quoted by Coffey (135), admitted that his operation did not cure constipation. Hurst (301), Flint (206), Dawson (161), and others all report that neither colectomy nor hemicolectomy cures constipation, or, if it does, it leaves the individual in a worse state than ever by converting the constipation into an uncontrollable diarrhoea. From this we may conclude that the caeco-colon is not an important factor in the production of constipation, an opinion also supported by radiological evidence.

Earlier observers like Schwarz (545) and Skinner (560) thought they could differentiate an atonic from a spastic type of constipation radiologically, but

Carman (110) and later observers all agree that whereas states of atonicity and spasticity are frequently observed radiologically they are not necessarily associated with constipation. Conversely, an obstinately constipated individual may present the picture of a normal functioning colon. Hence we must look to the distal end of the tract to explain the condition. King (350) has shown that stimulation of the skin area around the anus and the anal canal itself can inhibit intestinal movement. He suggests that haemorrhoids may be the cause of constipation and not constipation the cause of haemorrhoids. It is undoubtedly the case that the cure of many apparently trifling local conditions in the anal canal may result in the complete cure of a most obstinate constipation. Hurst (298), who has so exhaustively dealt with the subject of constipation, states that dyschezia is by far the commonest form. In the visceroptotic or chronic intestinal invalid he regards weakness of the abdominal muscles and of the pelvic floor as the most important factor producing inability to empty the rectum and pelvic colon. Clinical experience, however, shows that individuals with relaxed pelvic floor and atrophic abdominal muscles may have a regular bowel movement, and Kantor's figures quoted above show that asthenia plays little part in the production of constipation. Moreover, we meet with individuals of perfect physique and whose dietic habits are above reproach and yet who are constipated. An explanation of this anomaly would appear to lie in a consideration of the recto-sigmoid apparatus. Mayo (430) and Hurst (305) believe that this possesses a definite mechanism which retards the faecal current and prevents the continuous progress of the intestinal contents into the rectum. When the faecal column, which has been held up, enters the rectum the desire to defaecate is provoked. This reflex is established by means of the 'muscle' sense of the distended rectum, and initiates a mass movement which empties the rectum and part of the pelvic colon. Secondary mass movements occur and continue until under normal conditions the entire large intestine below the splenic flexure is completely emptied. According to Soper (567) the formation of faeces probably occurs in the iliac colon. This is particularly true of the fragmentary form of constipation, in which small hard round masses appear in the faeces. Soper finds that spasm or hypertonic contractures of the apparatus are a frequent cause of obstinate constipation.

Strangely enough he finds that atony of the apparatus may similarly be associated with constipation, and in cases where the apparatus appears to be absent, and there is no line of demarcation between rectum and pelvic colon, the constipation is exceedingly obstinate. Obviously, when spasm holds up the faeces in the pelvic colon inspissation will proceed to a maximum degree, so that eventually only a small feebly-stimulating stool will enter the rectum. In atony, on the other hand, the constant pressure of faecal material in the rectum would result in raising its threshold to such a degree that the defaecation reflex cannot occur without an abnormal stimulus. Two clinical observations support the theory that constipation in the chronic intestinal invalid is the result of spasm of the recto-sigmoid apparatus. Firstly, the institution of

a bland non-irritating diet plus the administration of sedatives often succeeds admirably in relieving the condition. Secondly, the intolerance of these patients to ordinary purgative medicine. A simple laxative either fails to have any effect on the patient, or else it produces intolerable griping without emptying the bowel properly. In milder cases paraffin succeeds, probably by reducing the colonic irritation. In severer cases paraffin fails, and if taken in sufficient quantity simply oozes from the anus without assisting in defaecation.

In the atonic type purgation equally produces griping, the result of irregular and incoordinate contraction of the colonic musculature, and these cases require a daily enema to wash out the colonic contents.

How this condition of spasm originates requires some explanation. Now Leube (395) many years ago pointed out that simple pressure of the finger in the rectum is often sufficient to produce immediately a series of symptoms in a sensitive individual which closely resemble those which are met with in the toxaemic patient. Alvarez (16) showed that a pressure of 2–3 mm. Hg is perceived by the rectum and that 20–60 mm. causes acute distress.

Donaldson (169), in a series of carefully-conducted experiments, showed that the symptoms presented by those seeking relief from constipation cannot be taken as unquestioned evidence of the absorption of toxins, and that in cases of ordinary constipation toxic substances are not necessarily absorbed in the blood, nor are they present in the faecal mass in sufficient amounts to produce symptoms if absorbed. His experiments revealed that the mechanical irritation of the pelvic colon and rectum are alone sufficient to produce the typical symptoms of autointoxication. He found that 'the nervous system was the distributing agency and that all tissues shared in the disquietful state, probably the result of endocrine lack of balance. Gee some years ago said that ' many of those who are continually complaining of constipation are suffering more from fear and hypochondria than from anything else. It is no law of Nature that the bowels should be relieved punctually once in twenty-four hours'. As we hope to show later, fear and anxiety is a common cause of spasticity. If an individual is harassed by the fear that the failure to obtain a daily evacuation is productive of bodily harm his anxiety only increases the spasm from which he seeks relief by purgation. To the muscle spasm is now added colonic irritation and a vicious circle results in which, in established cases, it is difficult to dissociate the mental from the physical.

Intimately associated with constipation in the chronic intestinal invalid is the condition now generally referred to as muco-membranous colitis. G. van Swieten, on page 193, Vol. I, of his *Commentaries upon the Aphorisms of Boerhaave* (London, 1744), quotes an account from Galen, in which the latter reports having experienced in his own person an attack of severe abdominal pain accompanied by the evacuation of much gelatinous material in the stool.

Van Swieten then proceeds to deal with the condition as if it were a manifestation of what we would call to-day the exudative diathesis. Morgagni (465) described the finding *post mortem* of gelatinous deposits on the intestinal

mucosa, but it is not until we come to Abercrombie (2) that we find a clear-cut picture of the clinical condition which Powell (502) later raised to the status of a clinical entity.   To this Good (239) gave the name of tubular diarrhoea, while Whitehead (559) termed it mucous affection of the intestines.

Sireday (559) was the first to suggest that the affection was a secretory neurosis rather than a true inflammation, and in this view he was upheld by Da Costa (155) in America.   Later observers were divided into three groups, some regarding it as a pure neurosis, others as partly neurosis and partly inflammatory, while a third held that the affection was an inflammatory eruption of the intestinal mucosa, very similar to the aphthous ulceration of the mouth, which is such a common symptom in the intestinal invalid.

Glenard was the first to suggest that muco-membranous colitis was not a clinical entity but simply one of the symptoms of enteroptosis.   de Langenhagen (386) pointed out that enteroptosis may be met with unaccompanied by muco-membranous colitis, and that colitis may be seen without enteroptosis; in the latter case the symptom is slight, whereas in all cases where it is prominent enteroptosis co-exists.   He was the first to indicate clearly the sequence of events: (1) Stubborn and prolonged constipation. (2) The sudden appearance of glairy discharge and membranes in the stool with pain.   (3) Intensification or appearance of functional disturbances of the stomach and nervous system, along with increased manifestations of enteroptosis. A few years later, Hurst (300, 304, 306) drew an analogy between it and asthma, and promulgated the view that the colon responded with over-secretion of mucus to similar types of nervous influences which in other cases produced asthma.   It is to be remembered that mucin is a normal constituent of the colonic contents. When this mucin, which contains no albumen or pus cells, is poured out in excess and retained in the bowel by spasm, it is then coagulated by mucinase so that, when finally expelled, it is passed in the form of a jelly or membrane.

Irritation from long-continued spastic constipation or from injudicious local treatment may result in a true inflammatory colitis being superadded to the original neurosis.   Dawson (161), however, has brought forward the most cogent evidence in support of the view that muco-membranous colitis is only one aspect of a disturbance which sweeps through the alimentary tract from end to end.   Sometimes this disturbance begins in the upper alimentary tract with an unpleasant taste in the mouth, furred tongue, red pharynx, epigastric pain, nausea and distension, to be followed, a few hours later, by the characteristic pain and passage of mucus.

In other cases griping pains and the passage of mucus appear first.   In one such case with an appendicostomy opening the colon was washed out at the first onset of symptoms.   The washing was found to contain undigested food, showing that the upper alimentary tract was disturbed even before the disturbance was appreciated by the patient subjectively.

He concludes that the most obvious source of such a widespread and, at the same time, apparently selective disturbance must be in the central nervous

system. From the evidence so far produced it is permissible to assume that muco-membranous colitis and constipation in the chronic intestinal invalid are simply manifestations of a disordered neuro-muscular mechanism.

More recently an attempt has been made to explain it by the theory of allergy on the same lines as the latter is used to explain asthma. Coca (131) has shown that allergy is a state different from anaphylaxis in three respects, in that (1) the exciting agent need not be antigenic, (2) it is based on a natural inherited make-up, and (3) the phenomena of desensitization is entirely wanting. Duke (179), Andresen (21), and others have reported cases of attacks of abdominal pain of obscure origin which disappeared after the removal of certain articles of food from the diet. They do not specify whether these attacks were accompanied by the passage of mucus, but Hollander (284) has reported six cases, all presenting the classical picture of muco-membranous colitis, in which the attacks disappeared after the taking of offending articles of food had been given up. The fact that many chronic intestinal patients are unable to tolerate certain articles of food is a well-established clinical observation, but whether the explanation of it is advanced in any degree by attributing it to the equally obscure condition of allergy is a moot point.

The Relationship between Physical Symptoms, Mental Reaction, and Constitutional Make-up.

The classical researches of Pavlov (*Conditioned Reflexes,* Lond., 1927) and Cannon (*Bodily Changes in Pain, Hunger, Fear, and Rage,* N.Y., 1915) have demonstrated the profound modifications in organ function which can be brought about in the healthy animal by a variety of emotional states. In the case of the digestive tract they were only offering an experimental demonstration of phenomena long recognized in the practice of medicine. Watson (616) summed up this clinical experience when he stated that there are habits of mind and habits of life which have no direct relation to the organs of digestion, and yet exercise a material influence over their function. Goodhart (240) went further when he wrote: 'If I were to write a book about indigestion, I should first devote myself to a volume on diseases of the nervous system. . . . The intestine is a highly sensitive organ from which we can often read the temperament and disposition of the man; it is an index of the state of nervous tone and vigour of the patient.'

A decade later and the radiologist had begun to read off from the screen the mental state of the individual whose gastro-intestinal tract was under investigation. Barclay (42) was amongst the first to observe a high transverse stomach suddenly loose its tone, so that the greater curvature dropped into the pelvis the moment the subject was suddenly startled by a door slamming. Horder (287) reported observing a similar result when the screen slipped upwards and struck the patient's chin. Langdon Brown (81) recorded the case of a nervous man called up for military service in whom the radiograph showed

atonic dilatation of the stomach. After the patient had obtained exemption his stomach was re-examined and was found to have regained both its tone and position. Some months later, when his exemption came up for review, the stomach had reverted to its atonic form. The most complete investigation of the effect of emotion on the gastro-intestinal tract in healthy individuals has been that undertaken by Todd (591). He examined a series of freshmen on their first day in the anatomy class and then a year later. Invariably the second radiograph showed a different picture from the first taken the year previously when the student's emotional state was one of bewilderment, with a certain degree of fear and anxiety. He found that all parts of the intestinal tract are exceedingly sensitive to emotional or nervous conditions. The stomach becomes atonic in outline, though not in movement or emptying time, as Kast (336) had previously observed. The duodenum shows pseudostasis. The transverse colon exhibits a spasm which may absolutely inhibit the onward passage of its contents. The cardia and pylorus drop, though not to such an extent as do the greater curvature, the pyloric vestibule, and the gastric tube. When there existed a spasm of the transverse colon the peristaltic waves in the lower ileum became exceedingly slow. Investigating individuals in a poor state of health Kast (336) found that, although both mental and physical exertion slowed the emptying time of the stomach, the mental state had the greater effect, even in a state of complete physical rest.

Ludlum (406) investigated the gastro-intestinal tract in a group of psychotics and found a direct relationship between the type of mental reaction and the physiological state of the gastro-intestinal tract.

Henry (274) repeated his investigation on a much more extensive group of cases which comprised every possible type of mental reaction, from the mildest psychoneurotic to the most profound psychotic. He found in depressed patients the greater the depression the greater the intestinal sluggishness. In chronic dementia praecox patients there was a tendency to return to normal gastro-intestinal functioning when they had succeeded in making some adjustment. Paranoid states showed a tendency to be associated with higher position and higher tonus of the hollow viscera than did praecox states, except in the region of the pelvic colon and rectum where hypomotility and hypotonicity was the rule. Psychoneurotics showed definite hypertonicity or even spasticity with hypomotility. Henry concludes that certain definite physiological visceral changes accompany and are intimately associated with different types of abnormal mental reaction. He suggests that the so-called normal variations in gastro-intestinal functioning, and even some gastro-intestinal states believed to be pathological, may be due, in part, to psychological variations met with in normal individuals.

In the case of the secretory curve, although it has been well established by both laboratory workers, and by clinicians like Hurst and Izod Bennett (302 and 59), that emotion can profoundly alter its character, this observation has little bearing on the explanation of subjective symptoms. The findings of Hurst (294) that the stomach is insensitive to the maximum HCl concentration ever observed

in life, and of Alvarez (11) that it is only when the gastric juice regurgitates to reach the sensitive lower pharynx that 'burning' is sensed by the patient, have found corroboration in the large number of cases of 'hyperchlorhydria' examined by the fractional method.   Many of these have a low acid titre, and those cases with high acid titres, without exception, fail to reveal any reduction in the acid content after the symptoms have disappeared and a clinical cure has resulted. Assuming then that gastro-intestinal function is to a large extent dependent upon mental factors, it is pertinent to inquire how this may be brought about. The dualistic concept of mind and body has been almost axiomatic in medical thought.   From this has been deduced that one of the functions of the mind is to distribute a certain amount of energy for the maintenance of healthy functional activity of the body.   In the case of the digestive system symptoms were supposed to arise when, in the words of Goodhart, 'energy necessary for digestion is consumed in other directions'.   This concept of the dissipation or exhaustion of nervous energy resulting in organ malfunction and symptom formation was popularized by Van Deusen (165) and Beard (54) under the term 'neurasthenia'.   It received the approval of Charcot (224) and other leading neurologists.   With the rise of modern psychopathology it was found that this simple concept of exhaustion was insufficient to explain the causation of the many new types of abnormal mental reactions which came to be isolated and identified.   First Charcot (224) separated the hysterical reaction, then Janet (322) the obsessional and the phobias, and finally Freud (214) the anxiety neuroses.   According to Jones (323), if a series of cases, in which the diagnosis of neurasthenia had been made, were submitted to exact analysis it would turn out that the majority of them were really cases of anxiety neurosis, obsessional neurosis, or of some form of hysteria; that many were mild or early forms of dementia praecox and manic depressive insanity; that a small proportion were toxic psychoses, early general paresis, or post influenzal depression; and that only a minimal number, fewer than one per cent., were really cases of neurasthenia.

When a group of chronic intestinal invalids is investigated on the psychological side, it at once becomes evident that no one single form of mental reaction is common to all; moreover, the reaction which is present is not, as a rule, of a type which would enable it to be readily classified.   Hysterical trends, obsessional trends, and so on, may be observed in individual cases, but there is no consistent association of one definite form of mental reaction with the physical state.   The most that can be said is that some departure from normal mental function is fairly regularly associated with the departure from normal physical functioning.   De Giovanni (225-7) was the first seriously to investigate the association.   According to him, it was not a case of there being several different neuroses, but rather a nervous diathesis, which could exhibit many clinical forms.   This diathesis resulted from a special constitutional organization.

In this view he was supported by Viola (604-5) who, from a study of 400 males in Northern Italy, found that the type of neurosis exhibited by an

individual depended upon the body build. According to him, all individuals are either microsplanchnic, macrosplanchnic or normal, a classification that corresponds to the narrow back, broad back, and normal of Goldthwait. He assumed that the autonomic and central nervous systems were both independent and antagonistic functional units. With the failure of the trunk to develop in the microsplanchnic, the autonomic system, which it housed, equally failed to develop and the central nervous system became dominant; on the other hand, in the macrosplanchnic, the autonomic system developed excessively and became dominant. In the normal there was a balance between the two systems. He concluded that the soil of a psychoneurosis is prepared by complex endogenous factors. These may appear externally under the aspect of morphologic disharmonies arising within the organism during its pre-natal life and during the period of development. Both the developmental and morphologic defects or excesses and the neurotic constitution have the same genetic basis. The microsplanchnic is a candidate for the asthenic forms of psychoneurosis because of the deficient muscular development and poor organic function which results from a faulty development of the autonomic nervous system. Conversely, the macrosplanchnic develop sthenic forms. Both the asthenic and sthenic forms differ from the 'pure' clear-cut types of neurosis found in individuals of normal build. However unsatisfactory this theory may be it was at least an attempt to justify the empirical observation that the ultimate character of an individual can often be estimated from his appearance. On this empirical observation was based the concept of 'constitution' as used by the physicians of an earlier period. After a somewhat prolonged eclipse, the study of the constitution has again come into its own from the assembling of four sets of data, those of photography, anthropometry, endocrinology, and psychiatry.

The most notable attempt is that of Kretschmer (363). He divides mankind into the athletes, the pyknic or well-nourished people, the leptosomic or asthenic people, and the dysplastics or victims of endocrine or other dysplasias. (Adler's inferiority complex.) Applying this classification to the psychoses, he found that two-thirds of manic depressive cases are of the fat-faced, ruddy, soft-bodied or pyknic type, while of the schizophrenic cases one half are pale asthenics, one-fourth athletes and one-fourth dysplastics. From this it follows that the organic or physical configuration and the functional or character traits of certain psychoses are probably not independent, but that there is a fusion of the psychic with the somatic. We have here apparently a definite correlation between facies, habitus, and mentality. The line of demarcation, however, is in no wise rigid, since, by the crossing of hereditary traits, a schizoid mentality may co-exist with a pyknic physique and vice versa. In women also the physical characteristics are less sharply defined than in men. Moreover, racial and social affiliations and environment in its widest sense may superinduce transient or permanent praecox traits, although the constitutional basis of character of another type remains unaltered. It has been even suggested that the body type itself may alter. Mollenhoff (457), for instance, claimed to find the asthenic type more

frequent among the young, and the pyknic more frequent in advancing age. Wertheimer and Hesketh (624) studied non-psychotic individuals in the light of Kretschmer's work. They find that in everyday life personalities are judged usually by the attitude they show towards the environment, and especially to other members of the social group. Certain persons obtain satisfaction chiefly through the affective reactions experienced from contact with their fellows. Not only do they react emotionally to the experiences of life, which entail co-ordination or disagreement with others, but they are always fundamentally in affective contact with their whole personal and social environment. Physically such individuals are pyknic, but these observers prefer to describe the mental reaction of the pyknic habitus by the term syntropic.

Others, however, find satisfaction in difference, in detachment, and in isolation from their personal and social environment. They obtain satisfaction, not from contact with other personalities, but from the interplay of their own mental experiences on the intellectual and imaginative levels. These latter tend towards an asthenic habitus, and their mental state is described as idiotropic. Mr. Pickwick with his pyknic habitus was of a syntropic temperament, while the long lanky Don Quixote undoubtedly possessed an idiotropic one. Clinical experience shows that whereas the chronic intestinal invalid may be of any body build, the severer degrees of invalidism are more likely to occur in those of an asthenic habitus. The demonstration of a direct association between asthenic habitus and an idiotropic mentality explains why so little can be done for the more severe degrees. The subjective sensations of malfunction in long-standing cases tend to invade and dominate the whole personality to such an extent that the patient is no longer able to get in touch with the psychological influence of the physician.

I fully recognize that much of the work done on constitution is uncritical, and that many of the types of body build recognized are largely subjective in character and not clearly defined in measurable terms, nor are they of necessity associated with ill-health. C. M. Jackson (317), for instance, has demonstrated in the case of healthy adults that conclusive evidence is lacking that the slender asthenic thorax is inefficient in function, or that the pulse-rate and blood-pressure are directly associated with habitus. Yet in the case of ill-health there is now sufficient evidence to suggest an association between habitus, a special mentality, and a tendency to intestinal malfunction of congenital and possibly inherited origin.

Although the young infant can scarcely be described as possessing either a habitus or a mentality, yet Finkelstein's work shows that in its reaction to normal food it may display an inherited weakness of structure and function at any period from birth to weaning. On the mental side such infants tend to sleep badly, are easily startled, restless and whining after the best possible digestive adjustment. In early childhood there appears in certain children symptoms which bear a striking resemblance to those of the adult intestinal invalid. The classical description of these was given by Eustace Smith (563)

under the term 'mucous disease', a term which has been replaced by chronic intestinal indigestion of children. Later observers have noted that these children tend to be tall for their age and of a slim build. Thus Seham (551) found in his cases that the child was on an average two inches taller, had five inches less chest circumference, and was 5 lb. under weight, compared with a normal child of the same age.

While all observers have noted its association with nervous symptoms, Cameron (103) has specially stressed the association of amyotonia, pallor, and ready exhaustion in these cases. The amyotonia leads to postural defects and an absence of that facial play and expression which is so characteristic of health. In severe cases there may be restlessness, with incoordinate movements of the small muscles of the face and hands; abdominal pain, vomiting, constipation, and 'negativism'. He regards these patients as candidates for the 'pexies' and 'ectomies' of adult life. Why many of these individuals attain normality while others indeed drift into the state of the chronic intestinal invalidism of adult life is best explained by the modern concept of 'constitution'. For the older physicians constitution was a fixed state which an individual brought with him from his embryonic state and which shadowed him throughout life. Kraus (362), one of the pioneers of the newer study of the constitution, demonstrated its dynamic nature in contradistinction to the old static view. He has pointed out that there are two factors in every individual, the genotype or the inheritance pattern, and the phenotype or the realized individual as he is at a particular moment. The phenotype is the result of a series of reactions between the genotype and the environment. If this be so, the constitution of an individual, as Stockard (580) pointed out, is actually a different thing at different life periods.

The final adult constitution is therefore a somewhat uncertain accomplishment which has been affected and influenced by both internal and external factors acting from birth. Draper (171–3) defines constitution as that aggregate of hereditary characters, more or less influenced by environment, which determines the individual's reaction, successful or unsuccessful, to the stress of the environment. According to modern biological thought there is something inherent in animal cells which drives them to divide, multiply, and differentiate into special organs. From this it follows that the course of life may be roughly marked off into three epochs, according to the changing relationship of viabiotic to necrobiotic forces. The capacity which cells possess of growing and developing in a fashion characteristic for a given species is laid down in the genetic plan and is probably passed on through the medium of the chromosomes. For Davenport (157) the phenotype is the up-to-the-instant result of hereditary forces or idiokinetic influences distorted by environment pressure or parakinetic influences. He considers that there is good reason to believe that the endocrine glands which exert such important effects upon growth are directly influenced by emotional stimuli. For example, fear in childhood, sense of inferiority at puberty, &c., may deflect the idiokinetic forces. So it comes about that when a patient consults a physician he inevitably presents a trinity of problems—the

in life, and of Alvarez (11) that it is only when the gastric juice regurgitates to reach the sensitive lower pharynx that 'burning' is sensed by the patient, have found corroboration in the large number of cases of 'hyperchlorhydria' examined by the fractional method. Many of these have a low acid titre, and those cases with high acid titres, without exception, fail to reveal any reduction in the acid content after the symptoms have disappeared and a clinical cure has resulted. Assuming then that gastro-intestinal function is to a large extent dependent upon mental factors, it is pertinent to inquire how this may be brought about. The dualistic concept of mind and body has been almost axiomatic in medical thought. From this has been deduced that one of the functions of the mind is to distribute a certain amount of energy for the maintenance of healthy functional activity of the body. In the case of the digestive system symptoms were supposed to arise when, in the words of Goodhart, 'energy necessary for digestion is consumed in other directions'. This concept of the dissipation or exhaustion of nervous energy resulting in organ malfunction and symptom formation was popularized by Van Deusen (165) and Beard (54) under the term 'neurasthenia'. It received the approval of Charcot (224) and other leading neurologists. With the rise of modern psychopathology it was found that this simple concept of exhaustion was insufficient to explain the causation of the many new types of abnormal mental reactions which came to be isolated and identified. First Charcot (224) separated the hysterical reaction, then Janet (322) the obsessional and the phobias, and finally Freud (214) the anxiety neuroses. According to Jones (323), if a series of cases, in which the diagnosis of neurasthenia had been made, were submitted to exact analysis it would turn out that the majority of them were really cases of anxiety neurosis, obsessional neurosis, or of some form of hysteria; that many were mild or early forms of dementia praecox and manic depressive insanity; that a small proportion were toxic psychoses, early general paresis, or post influenzal depression; and that only a minimal number, fewer than one per cent., were really cases of neurasthenia.

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alter. Mollenhoff (457), for instance, claimed to find the asthenic type more

frequent among the young, and the pyknic more frequent in advancing age. Wertheimer and Hesketh (624) studied non-psychotic individuals in the light of Kretschmer's work. They find that in everyday life personalities are judged usually by the attitude they show towards the environment, and especially to other members of the social group. Certain persons obtain satisfaction chiefly through the affective reactions experienced from contact with their fellows. Not only do they react emotionally to the experiences of life, which entail co-ordination or disagreement with others, but they are always fundamentally in affective contact with their whole personal and social environment. Physically such individuals are pyknic, but these observers prefer to describe the mental reaction of the pyknic habitus by the term syntropic.

Others, however, find satisfaction in difference, in detachment, and in isolation from their personal and social environment. They obtain satisfaction, not from contact with other personalities, but from the interplay of their own mental experiences on the intellectual and imaginative levels. These latter tend towards an asthenic habitus, and their mental state is described as idiotropic. Mr. Pickwick with his pyknic habitus was of a syntropic temperament, while the long lanky Don Quixote undoubtedly possessed an idiotropic one. Clinical experience shows that whereas the chronic intestinal invalid may be of any body build, the severer degrees of invalidism are more likely to occur in those of an asthenic habitus. The demonstration of a direct association between asthenic habitus and an idiotropic mentality explains why so little can be done for the more severe degrees. The subjective sensations of malfunction in long-standing cases tend to invade and dominate the whole personality to such an extent that the patient is no longer able to get in touch with the psychological influence of the physician.

I fully recognize that much of the work done on constitution is uncritical, and that many of the types of body build recognized are largely subjective in character and not clearly defined in measurable terms, nor are they of necessity associated with ill-health. C. M. Jackson (317), for instance, has demonstrated in the case of healthy adults that conclusive evidence is lacking that the slender asthenic thorax is inefficient in function, or that the pulse-rate and blood-pressure are directly associated with habitus. Yet in the case of ill-health there is now sufficient evidence to suggest an association between habitus, a special mentality, and a tendency to intestinal malfunction of congenital and possibly inherited origin.

Although the young infant can scarcely be described as possessing either a habitus or a mentality, yet Finkelstein's work shows that in its reaction to normal food it may display an inherited weakness of structure and function at any period from birth to weaning. On the mental side such infants tend to sleep badly, are easily startled, restless and whining after the best possible digestive adjustment. In early childhood there appears in certain children symptoms which bear a striking resemblance to those of the adult intestinal invalid. The classical description of these was given by Eustace Smith (563)

under the term 'mucous disease', a term which has been replaced by chronic intestinal indigestion of children. Later observers have noted that these children tend to be tall for their age and of a slim build. Thus Seham (551) found in his cases that the child was on an average two inches taller, had five inches less chest circumference, and was 5 lb. under weight, compared with a normal child of the same age.

While all observers have noted its association with nervous symptoms, Cameron (103) has specially stressed the association of amyotonia, pallor, and ready exhaustion in these cases. The amyotonia leads to postural defects and an absence of that facial play and expression which is so characteristic of health. In severe cases there may be restlessness, with incoordinate movements of the small muscles of the face and hands ; abdominal pain, vomiting, constipation, and ' negativism '. He regards these patients as candidates for the ' pexies ' and ' ectomies ' of adult life. Why many of these individuals attain normality while others indeed drift into the state of the chronic intestinal invalidism of adult life is best explained by the modern concept of ' constitution '. For the older physicians constitution was a fixed state which an individual brought with him from his embryonic state and which shadowed him throughout life. Kraus (362), one of the pioneers of the newer study of the constitution, demonstrated its dynamic nature in contradistinction to the old static view. He has pointed out that there are two factors in every individual, the genotype or the inheritance pattern, and the phenotype or the realized individual as he is at a particular moment. The phenotype is the result of a series of reactions between the genotype and the environment. If this be so, the constitution of an individual, as Stockard (580) pointed out, is actually a different thing at different life periods.

The final adult constitution is therefore a somewhat uncertain accomplishment which has been affected and influenced by both internal and external factors acting from birth. Draper (171–3) defines constitution as that aggregate of hereditary characters, more or less influenced by environment, which determines the individual's reaction, successful or unsuccessful, to the stress of the environment. According to modern biological thought there is something inherent in animal cells which drives them to divide, multiply, and differentiate into special organs. From this it follows that the course of life may be roughly marked off into three epochs, according to the changing relationship of viabiotic to necrobiotic forces. The capacity which cells possess of growing and developing in a fashion characteristic for a given species is laid down in the genetic plan and is probably passed on through the medium of the chromosomes. For Davenport (157) the phenotype is the up-to-the-instant result of hereditary forces or idiokinetic influences distorted by environment pressure or parakinetic influences. He considers that there is good reason to believe that the endocrine glands which exert such important effects upon growth are directly influenced by emotional stimuli. For example, fear in childhood, sense of inferiority at puberty, &c., may deflect the idiokinetic forces. So it comes about that when a patient consults a physician he inevitably presents a trinity of problems—the

disease process, the malevolent external agent, and the man himself. The aphorism that to secure good health and a long life a man should choose his parents wisely has received abundant proof from the biometrical studies of Pearl (494). Yet though 'we are woven out of the warp and woof derived by the mitotic division of two parental sex cells making a garment infinitely finer in texture and more intimately blended in its structural elements than any fabric', De Beer (57) reminds us that heredity does not account for the individual but merely for the potentialities, some of which are realized from the action of external stimuli. Hence it is not sufficient to postulate the existence in the germinal chromosomes of genes corresponding to the cycloid, schizoid, and other *anlages* of Kahn (328), Hoffman (281), and Barrett (43), since a suitable mental environment is just as necessary for the development of mental characters as a suitable physical environment is for the development of physical characters. As individuals develop they tend to choose their own mental environment according to their own inherited tastes and aptitudes. Since mental environment is extremely complex and intimate in the way it impinges upon the developing organism, it will have a much greater importance in determining the final mental state than the physical environment. But where the inherited potentialities are not strong enough to enable the individual to choose his own environment, then we find environmental stresses distorting the mental and physical, and producing an association more apparent than real. When the normal course of mental development is deviated or distorted, the end result may be observed, according to Meyer (447), on one of three levels, the vegetative, reflex, or psychological, depending on whether it reveals itself through the action of the visceral organs, the sensori-motor system, or the complete personality as a whole. If we now assume as a part of the physical environment an inherited physical defect as may be presumed to exist in dysplastics like the marasmic infant, the nervous child of Cameron, the child with chronic fatigue of Seham, &c., we have then the state of affairs to which Adler (5) called attention, namely, organ inferiority, with all its potential psychical consequences. As is well known, Adler traces all forms of neuroses to a feeling of inferiority based on some actual organic defect. According to him an individual, possessing such a defect and becoming more or less clearly aware of it, acquires a feeling of inferiority which he attempts to disguise. His main purpose or goal in life then becomes set in the direction of compensating for this defect and so overcoming the feeling of inferiority. In some cases the effort is successful, but more often it fails. In the latter case the individual takes flight from reality and develops symptoms, which he uses as an excuse for his failure to attain the superiority he secretly desires. The symptoms justify him abandoning the role of a useful member of society and securing for him in the domestic circle the attention which is denied him in the wider social world.

It is to be regretted that Adler did not pursue this important line of investigation. Unfortunately the examples he gives in his book are not so convincing as they might be if he had concentrated upon the digestive system.

The intimate connexion between the mental and physical phenomena observed in chronic intestinal invalidism can best be explained by the Adlerian theory which, after all, seems but to be a special application of failure in adaptation. As Ruggles Gates remarks, in *Nature* of 6 November 1926, one of the most remarkable things about healthy organisms in general is the stability they often show under altered conditions of development, both in the physical and the mental characters, and their power at the same time to adapt themselves to these altered conditions, if it is to their advantage to do so. C. P. White (626) has pointed out that adaptability is one of the three fundamental principles of life. None the less its range varies greatly from individual to individual. On the one hand, we have the type of case reported by Murray (477), where a patient with a grave organic lesion falsifies the gloomiest prognosis as regards life and efficiency by leading an active, useful, and happy existence long beyond the span prophesied for him. On the other, some of the worst cases of chronic intestinal invalidism lapse into a vegetative life without presenting any lesion recognizable by the pathologist. Dawson (161) suggests the chain of events in intestinal invalidism originates in a congenital, over-responsiveness of the abdomen to nerve impressions. In these individuals fatigue, fear, anxiety, and intensive endeavours manifest themselves in their hollow viscera as disturbances of rhythm, motility, and secretion. These in turn lower the threshold of the nervous system until slighter and slighter disturbances become perceived. A state of mind is then added to a state of body, and the individual is reduced to a condition in which the mind is completely subjected to bodily sensations. This view seems too narrow if the claim be substantiated that it is possible to recognize in infancy and in childhood the onset of the condition, or as Cameron puts it, ' to see these children as they grow to adult age become candidates for the operation of colectomy or colopexy '. Nor does the theory of the over-responsive abdomen explain the symptoms outside the gastro-intestinal tract, the 'status catarrhalis', the amyotonia, pallor, albuminuria, irregular temperature curve, &c., of children ; the fibrositic, the menstrual, and other associated symptoms of adults. The only theory which appears to cover all possible variations of the symptom complex is the theory of constitutional inadequacy. By this is meant a state of physical and mental make-up, congenital, and possibly inherited, which handicaps the individual in his adjustment to the various environmental stresses, using environment in its widest sense. As Hyslop (314) puts it, these individuals are like poorly constructed automobiles, made out of ' spare parts ' and poorly assembled, who go clanking through life. Prolonged observations of the chronic intestinal invalid invariably reveals departures from normal functioning in regions outside the gastro-intestinal tract. Some of these have long been recognized as the ' visceroptotic habitus ', the postural defects, &c., &c. Associated with these various disorders of body function, it is the rule to find the individual emotionally unstable, with a reduced capacity for intellectual effort, and an inability to assume responsibility. We find that adolescence and the climacterium are passed through with much greater

difficulty than in normal individuals.   Finally vasomotor, circulatory, endocrine and other disturbances almost invariably appear at some time or other.   All this is but a restatement of an old viewpoint.

Many years ago Clifford Albutt (8) described life itself as a series of physiological processes, of which 'diseases' and period of good health may be regarded as 'phases or modes of growth'.   He concluded that morbid states are but members or terms of a series though commonly diagnosed and treated in practice as independent self-limited diseases.

Charcot (122) insisted that the condition of the patient is only an accident in the history of the disease, just as each individual is an accident in the history of humanity.   Evidence in support of this was given by Sir James Mackenzie when he stated that not more than one-third of all patients who complain of symptoms can be assigned to a definite diagnostic group.   Rowland (533), working at the James Mackenzie Institute, found that out of a total of 974 private and hospital patients, no less than 49·48 per cent. fell into the group reserved for cases showing uncoordinated symptoms with no recognizable cause.

When we survey such a diverse group of conditions as general nervousness, so-called chronic appendicitis, the gastric neuroses, 'intestinal toxaemia', hay fever, asthma, paroxysmal rhinorrhoea, painful flat foot, and the so-called rheumatism of the 3–4 decades, dysthyroidism, neuro-circulatory asthenia &c. there is, in Osler's words (488), a positive advantage in recognizing the affinities and the strong points of similarity in affections usually grouped as separated diseases.   For by recognizing the affinities we seek for some unifying factor underlying the whole, and realize the futility of a therapeusis devoted solely to the one or other system where the symptoms happen to predominate.   The only unifying factor amidst such diversity is a constitutional inadequacy, manifesting itself in all systems, but more pronounced in one than another.   When the degree is greater in the digestive system than elsewhere symptoms will tend to appear early, since for normal growth it must work at continuous high pressure. Circulatory malfunctioning will not tend to appear until the emotional stresses of puberty and early adult life make themselves felt, while the muscles and joints may succeed in disguising their deficiency until the viabiotic forces have become equalized by the necrobiotic ones of late middle life.   In all such individuals, a more or less inadequate mentality is trying to adjust itself to the handicap of poor physical function.   According to the degree of mental handicap the individual may either triumph over, accept, or become the victim of his physical inefficiency.

Without relaxing any efforts to improve the physique of the child born or unborn, it should not be forgotten that some of the great figures in history, as well as a host of unknown if no less efficient workers, have triumphed over physical imperfection through a mental adjustment to their difficulties.

The Clinical Condition. Symptoms and Treatment.

THE following clinical observations are based on the study of a series of cases observed in general practice. When the notes of 1,200 consecutive patients were examined, it was found that 152 had sought advice for the relief of symptoms which centred round the gastro-intestinal tract, symptoms which, in Mackenzie's words, were uncoordinated, and for which no recognizable cause could be found. These patients fell into two groups. One group, 41 in number, had already received investigation and treatment without obtaining relief before coming under my care. They may be regarded as presenting the condition in its established, chronic form. The other group, 111 in number, consisted of individuals seeking advice for the first time, and therefore presenting a diagnostic as well as a therapeutic problem.

For this reason I propose to consider the two groups separately : the first group, to illustrate the symptoms and physical findings when the condition has permanently established itself resistant to treatment ; the second group, to elucidate the diagnosis and the prevention of chronic invalidism supervening in cases recognized early.

Group I.   This group consists of five males and thirty-six females.

Symptoms.

The four cardinal symptoms of this group were general weakness, abdominal discomfort, constipation, and flatulence.

General Weakness.   The patients state that the illness began with a gradual failure of energy, both mental and physical.   Before this onset they claim, as a rule, to have been quite well in mind and body.   Close questioning reveals the fact, however, that they had never been quite like their associates ; never capable of the same amount of sustained work, physical or mental, although at times capable of an intensive effort which surpassed even the best of their more robust friends.   Then they noticed a lessened ability to make this same effort, and they began to realize that they had fallen below their own average standard of endurance.   I found in the whole forty-one cases that this state of affairs had existed for a longer or shorter time before the development of other symptoms.   It was not until other symptoms had developed that they sought advice; in consequence, this general weakness had come to be looked upon, by both the patient and the physician, as something which had followed in the train of the other symptoms instead of preceding them.   With the realization of their inability to 'rise to the occasion', a certain degree of mental depression follows, and a mental searching for a physical explanation then begins.   With the development of further symptoms, and the fixation in the mind of a 'cause' for the general weakness, the latter tends to grow worse, producing a slowly, but steadily increasing incapacity to lead a normal life, physically, intellectually, or emotionally.   Four stages may be observed in this downward progression.   In

the first stage, the physical effort alone fails; in the second, both physical and mental effort is a failure with the will-to-do unimpaired; in the third, the will disappears; and finally, the individual lives in and for her symptoms. She then becomes strangely indifferent to losing everything that makes life worth living for the normal individual, and appears to find complete satisfaction in the submissive attention and sympathy of her relatives. More rarely, instead of becoming a torment to her friends, she adopts such an attitude of humble resignation that she seems to continue living solely from a sense of duty.

Strangely enough, even the most 'exhausted' cases can at times act energetically when some dominant emotion comes into play. For example, one *patient* with a strong 'fixation' on her father, whose death dated the onset of her illness, never fails to visit his grave on the anniversary of his death, although she spends the greater part of the year in bed as a confirmed invalid. On one occasion, taking a sudden dislike to her room, she was able to rise and assist in the removal of the furniture, &c., to another, working for six hours continuously, although usually she was unable to maintain the erect posture for longer than half an hour at a time. Again, those who find that they are quite unfit for the lightest household duties can often play tennis for a whole afternoon without fatigue. This apparently irrational behaviour suggested in several cases the adoption of a hectoring attitude as a therapeutic measure. The result is usually unfortunate. Quite submissively they will carry out instructions to behave like a normal individual only to retaliate in a few days with a severe attack of mucous colitis. The rarer submissive type of exhausted patient equally astonishes the observer at times. One of these nursed her husband day and night for six months until his death from malignant disease, although before and after she had to spend the greater part of each week in bed.

There seems to be an almost inverse relationship between exhaustion and other symptoms. The individual who is continually seeking relief for an ever-fresh pain or abnormal sensation is usually so active in this pursuit that weakness or exhaustion can hardly be said to exist. On the other hand, in the one who is 'too tired even to think', pains and abnormal sensations tend to sink into the background. Though these states may alternate in the same person the patient, as a rule, remains true to type—the 'painful' being always 'painful', and the 'exhausted' always 'exhausted'.

There is no relationship between body weight and the sense of weakness. Not infrequently a moderately thin person will declare that she always feels worse when she starts to put on a little extra weight.

Abdominal Discomfort. The variety of abnormal sensations arising from the abdominal organs in these forty-one *patients* is beyond description. For practical purposes they may be divided into two groups, painful and non-painful. In the present series, where the condition is long standing, true abdominal pain is conspicuously absent. The majority state that at the beginning of the illness they had suffered severe pain in one or other region of the abdomen; but since they have been under my observation this has not been

a prominent feature.   Attacks of acute pain in the right iliac fossa with a palpable tender caecum have been observed in five women from time to time. Acute pain in the left iliac fossa with a tender, palpable, contracted pelvic colon has been similarly observed in seven.   Two patients have repeated attacks of severe pain in the left hypochondrium, with vomiting and prostration lasting from six to forty-eight hours.   Four patients, two men and two women, have attacks of severe epigastric pain which, as a rule, come on at night shortly after the patient has fallen asleep.   Immediately following the onset of the pain there is a feeling of suffocation, accompanied by dyspnoea and palpitation. This lasts for twenty to thirty minutes, when relief is obtained with the eructation of gas and a little of the stomach contents.   Far more commonly the chief complaint is of some abnormal sensation continuously present.   The commonest is a dragging sensation, either in the epigastrium, in one or both iliac fossae, or in the umbilical region.   In the majority this is accompanied by a constant ache in the lower lumbar region, or over both sacro iliac joints.   In fact, it appears to me that in many of these cases there is an actual relaxation of the sacro-iliac joints, since frequently greater relief is obtained by a firm sacro-iliac support than by the usual abdominal belt.   Next to a 'dragging' is a burning, boring, or tearing sensation along the line of the colon, quite independent of an actual attack of membranous colitis.   With the onset of the latter true colicky pains supervene, though not infrequently large masses of membrane may be passed without any colicky pains being present.   Finally, the patient may complain of a sense of burning or itching, not located in the abdominal cavity but under the skin.   As I have already remarked, the sensations are described largely in terms of the imaginative powers of the individual, but on final analysis they fit into one or other of the above classifications.

It is very difficult to explain on a physiological basis the pains and abnormal sensations complained of by these patients.   In fact our knowledge of visceral sensibility is very incomplete, and in the case of the gastro-intestinal tract 'it is not clear whether powerful peristaltic waves alone give rise to pain or whether stretching of the hollow viscus is adequate too.   As a rule, of course, the two phenomena are associated together' (S. Wright, *Applied Physiology*, Lond., 1926, p. 110).   Now, in these cases powerful peristaltic waves are absent, at least in anything like the degree observed in organic obstruction.   It is true that a distended caecum or sigmoid loop is frequently detected, but gentle palpation, as a rule, causes the distended segment to empty itself without producing any relief of the pain.   Mackenzie's theory of an irritable focus seems the best explanation so far offered.   He assumes that if abnormal impulses constantly enter a certain region of the spinal cord it becomes modified in some unknown way so that the intensity of any impulses entering it becomes increased.   The extent to which the sensations vary under emotional influences suggest that these regions in the cord may be influenced also from above.   In severe cases the threshold of sensibility appears to be so low that the individual becomes aware of normal gastro-intestinal movement.   Any

sensation of which normally we are unconscious invariably carries with it an unpleasant-feeling tone when it enters consciousness. This unpleasant-feeling tone may in time influence the spinal segments and make them so irritable that sensations from the viscera, which would cause in a normal individual nothing worse than a vague discomfort, produce in these patients the severe pain and discomfort of which they so bitterly complain. The fact that no two patients describe their sensations alike suggests that their interpretation rests more on a psychical than on a physical basis. On the other hand, where there is a well-recognized physical basis, as for example peptic ulcer, the description of the pain is remarkably consistent from case to case. Finally opium, which so readily relieves organic pain before its sleep-producing effect comes into action, is singularly inert in relieving these individuals. As in most cases of psychical distress, small doses make them more excitable, and large doses send them to sleep, with the pain persisting to the last moment of consciousness.

Flatulence. Although the presence of an abnormal quantity of gas in the stomach and intestine may be associated with one or other of the above-mentioned pains it is not necessarily so. A patient may complain of a feeling of extreme distension without feeling any particular pain, even when the abdomen is visibly distended. Except for its association with pain in the right iliac fossa or epigastrium, flatulence chiefly incommodes by the necessity for constant eructation, or by its passage per anum or by borborygmi. In those able to get about the accumulation of gas may interfere with the wearing of corsets, &c. All these manifestations of flatulence are very noticeably produced by emotional upsets rather than by any dietetic or other indiscretions. Even in their severer forms they rarely last longer than a few days at a time. In three patients with excessively thin abdominal walls and marked separation of the recti, visible peristaltic movements of the small intestine and continuous eructation of gas from the stomach can be produced and maintained by lightly palpating the abdomen.

Constipation. If we accept Hurst's definition that it is a condition in which none of the residue of a meal, taken eight hours after defaecation, is excreted within forty hours, constipation was present in every one of this series. None of them was able to obtain a natural bowel movement without assistance. In 32, including all the males, the delay was definitely at the lower end of the colon, either above or below the recto-sigmoid apparatus. In 20 of these not only did X-ray examination show no delay elsewhere but the bulk of the bismuth meal was evacuated within 24 hours. In the remaining 12 there was a delay of the meal in the rectum longer than 24 hours, but the bulk had left by the end of 48 hours. This observation tends to support the view of many radiologists that the bismuth meal has a very definite laxative effect. All these patients were very intolerant of a failure to secure a daily bowel movement. Such failure was immediately followed by the onset of the so-called toxaemic symptoms; these disappeared at once with a satisfactory evacuation. Such individuals are inclined to inspect closely their evacuations, and unless they are

satisfied with the character and quantity passed they become distressed in mind. Five claimed to notice their skin grow muddy if longer than twenty-four hours elapsed without a satisfactory evacuation. In contradistinction to this group, nine showed but little accumulation in the rectum, even after several days had elapsed without an evacuation. In these cases an enema would bring away a quantity of small, discrete, hard nodules.

It appears likely that this nodule formation takes place throughout the length of the colon by excessive absorption of moisture, the result of a true colonic stasis. Yet X-ray examination failed to reveal any delay in the passage of the opaque material through the colon. The members of this group presented no 'toxaemic' symptoms and were perfectly definite that they felt much more comfortable when the bowels did not act. In fact, an action was always associated with a feeling of faintness and a sense of irritation along the line of the colon. They seemed to be torn between the comfort they secure by not having the bowels opened and the greater discomfort they will experience the longer they delay in securing an evacuation. A delay in these individuals is always associated with much mucus accummulation round the hard nodules, probably the result of a true colitis from the irritant action of the dry hard faeces on the intestinal mucosa. Such patients are very intolerant of purgation or even roughage in the food. A purgative either produces severe griping and no evacuation, or else a succession of painful, watery stools, which fail to remove all the hardened nodules. Yet, strangely enough, emotional stimuli often secures for them a satisfactory evacuation. Three of them are quite definite that the only time they have a natural bowel movement is on the day they expect a visit from their medical attendant. This form of constipation does not appear to be a sequel of the former, but a form, sui generis, which once established requires a daily enema for its successful treatment. It is possible to recognize the condition before it becomes permanent, whereupon the institution of a bland non-irritating diet and the administration of sedatives will often save them from the enema habit.

Apart from these four cardinal symptoms, all the individuals in this group display other departures from normal functioning, which in their order of frequency are as follows:

(1) *Fibrositis, Myalgia, Muscular Rheumatism.* Although 'rheumatism' is an extremely common condition amongst the general population, and not limited to any one section of the community, it seems to be especially severe and persistent in the chronic intestinal invalid. Of the forty-one, all suffer from it, not only in the form of definite acute attacks but also as a continuous discomfort which never leaves them, and which responds to atmospheric changes so accurately that many patients regard themselves, not unjustly, as veritable barometers. A particular distressing form is a severe aching behind the eyes with the sensation as if the upper lids were firmly retracted. The intercostal, pectoral, and occipital muscles are rather more frequently the site of pain than in a similar number of cases without intestinal symptoms. Those with the

most persistent occipital fibrositis complain of tinnitus, which waxes and wanes *pari passu* with the fibrositic pain. This suggests the possibility of a fibrositis of the small muscles of the ear being the cause of the tinnitus in these cases.

(2) *Susceptibility to Catarrhal Infections.* Not only do these patients appear to be much more susceptible to the catarrhal infections of winter and spring than normal individuals, but they may pass through several attacks in succession during the one season. Each attack is characterized by high temperature and great prostration, with a total absence of physical signs or complications. Strangely enough, during such attacks, their intestinal symptoms recede into the background, and it is only with the establishment of convalescence that these reassert themselves.

(3) *Pyrexia.* About one quarter of this series runs, from time to time, a mild pyrexia of 99–100 F, commencing and subsiding without any known cause and without any obvious association with particular symptoms. In none of these has repeated examination succeeded in revealing a tubercular or other focal infection. One patient who died of acute miliary tuberculosis never presented this type of pyrexia. Another quarter has a temperature curve subnormal in type and without the daily fluctuations of health.

(4) *Digestive Disturbances.* The appetite appears to be less disturbed than would be expected from the severity and persistence of the abdominal symptoms. There is no true anorexia apart from deliberate exclusion of certain articles of food believed to be the cause of the intestinal distress. This exclusion, by the way, may be carried to such lengths that a bare subsistence diet is finally reached. But in the majority the appetite remains surprisingly good throughout. Attacks of 'indigestion' occur but the patient as a rule does not associate them with any cause other than the state of the bowel. Investigation, however, seldom fails to reveal an emotional disturbance as the true cause of these attacks. Similarly, when a particular article of food is strongly stressed as a cause of stomach symptoms, an emotional factor is invariably found to be associated with that article in the mind of the patient. Stomach symptoms, when present, differ from those of organic disease chiefly by the extreme variability they display in relation to food, time of onset, method of relief, &c. When once invalidism has become established, true stomach symptoms tend to recede into the background, although in three quarters of the patients no longer troubled by indigestion the only original symptoms at the onset were definitely confined to the stomach. In only a quarter did bowel symptoms predominate at the beginning. In the early stages attacks of vomiting occurred, but later this tends to disappear. A furred tongue was present in only three quarters of the cases; in only three of these was there a disagreeable odour from the breath. Recurrent herpetic eruptions of the buccal mucosa occur in six, the stomatitis neurotica chronica of Jacobi.

(5) *Muco-membranous Colitis.* Every one of the forty-one cases have had at some time or other attacks of acute abdominal pain associated with the passage of mucus. Only in three, all women, do these attacks still recur with any degree of frequency. One has an attack about every six weeks, while the other

two usually have an interval of three to four months between each. Half of the cases had intervals of one year, while in the remainder they are still longer. In only five cases were these attacks prominent at the onset of symptoms. In the majority they did not commence until the other symptoms had been established for a period of twelve to eighteen months.

(6) *Vasomotor Symptoms.* All these patients present a very definite instability of the vasomotor system. Attacks of tachycardia and palpitation are very common. Cold hands and feet, with attacks of blueness and tinglings in the fingers and toes, are equally common. Attacks of vertigo, dizziness, and flushing also ·occur apart from the climacterium, and they are frequently brought about by a sudden movement from the reclining to the erect position. Attacks of paroxysmal rhinorrhoea occurred in five, and of typical angioneurotic oedema in two.

Apart from these two patients with attacks of oedema occurring in the classical positions, no less than ten others have attacks localized to the orbital region with discolouration of the skin affected. At one time it assumes the guise of an acute inflammatory process affecting both the lids and the circumorbital tissues. After a few days the bright red colour alters to a reddish blue, and in some to a definite ' black eye ', before the condition completely subsides. At another time it may remain bright red throughout, or finally it may appear reddish blue or bluish black from the beginning. One attack usually lasts ten days, and weeks or months may elapse before another occurs. More rarely there may be a series of attacks in succession, a fresh one developing before the previous one has completely subsided.

The remaining symptoms observed in this group may be summarized briefly. Delayed puberty, menstrual irregularities, dysmenorrhoea, and a persistent leucorrhoea was found in no less than 95 per cent. of the women. Yet ten patients who suffer severely from dysmenorrhoea obtain complete relief from their constipation during menstruation. Three of these patients have typical attacks of membranous dysmenorrhoea, passing at times complete casts of endometrium. Pyelonephritis due to *B. coli* infection occurred only once in this series. If, as it is generally assumed, infection of the kidney is via the bowel, pyelitis ought to be much commoner in a group of intestinal invalids than in a control group. On the other hand, what is more likely, disordered bowel function is probably no index of an increased infectivity or virulence of the intestinal organisms although, as Dudgeon shows, it may be accompanied by an increase in their number. Attacks of asthma replaced abdominal symptoms from time to time in two men and five women. True migraine was present in five women. Tinnitus was a troublesome symptom in as many as twenty women, but only two present the signs of otosclerosis. Insomnia of a more or less severe degree was complained of by 75 per cent. The remaining 25 per cent. state they can never secure a 'natural' sleep; that is, they claim to be either very restless, or sleep so heavily as to awake 'dazed' in the morning.

Eight of these patients are troubled from time to time by 'fugues'. They

waken up at night feeling that everything is unreal. At first mildly interested, the patient quickly becomes alarmed and tries to call out but cannot utter a sound. Neither can she move a muscle to convince herself that she is 'alive and not dead' as many put it. To the patient, the condition seems to last for hours, but it is obviously impossible to obtain precise information on this point. In one patient, who had attacks in the day time, I was able to time it, and found it lasted about thirty-five minutes. During this time the patient lay in a trancelike condition, but from her statements after the attack had passed was conscious of all that went on. These attacks are not confined to severe degrees of intestinal invalidism since they were present in five of my second group of cases. What is common to all the patients experiencing these attacks is the existence of severe mental conflict. This suggests that they really represent a dissociation syndrome.

Physical Findings.

Body Build. When I became first interested in the chronic intestinal invalid I had assumed that an asthenic build was a *sine qua non* for the diagnosis. But before reading the more recent literature on the relationship between body build, visceral position, and gastro-intestinal function, I was satisfied from clinical observation that no necessary relationship existed between symptoms and habitus. Chronic gastro-intestinal malfunctioning is met with nearly as frequently in the hypersthenic, and certainly in the sthenic, as in the asthenic individual. On the other hand, what is brought out by a review of the 41 cases is that the degree of invalidism bears a certain relationship to the build. Of the five men, one was hypersthenic, one sthenic, and three asthenic in build. Of the thirty-six women, only seven presented the classical figure of the visceroptotic habitus of the virginal type, and in only three that of the maternal type. Of the remaining twenty-six, twenty differed in no way from the average standard, while six were definitely hypersthenic in build. As regards invalidism, and the amount of incapacity resulting, the three asthenic men, the seven asthenic women of the virginal type, and two of the hypersthenic type very definitely showed a much greater degree than the remainder. This suggests that while all types of body build may suffer from gastro-intestinal malfunctioning, invalidism tends to be more severe and more persistent in the asthenic.

Radiological Examination of the Gastro-intestinal Tract. All these individuals have had radiological examinations at one time or other. On comparing the present clinical condition of each with the radiograms taken some years previously, it is clear that the latter were of value only in a negative sense by helping to exclude organic disease.

This is what is to be expected from a consideration of the more recent work which has revolutionized the time-honoured conceptions of the form and position of the abdominal organs. Several of the cases, whose original radio-

grams showed the hollow viscera considerably displaced from what was considered the normal, have responded much better to treatment than those whose radiograms, not once, but several times, had shown the viscera to be well within the limits of normality.

None of them showed any delay in the onward passage of an opaque meal. The times of stomach emptying were as follows:

	Male.	Female.
Empty within 2 hours	2	5
„ „ 3 „	2	30
„ „ 4 „	1	1

It is to be noted that in the seven cases with quickest emptying time epigastric pain and distress were more pronounced and persistent than in the others. This suggests that the normal 'hunger' contractions, on account of a lowered threshold of sensibility, tend to rise to consciousness and to be interpreted as abnormal sensations. Also, in the remainder of the tract no delay was observed; even the most pronounced cases of rectal constipation have evacuated the bulk of the meal in forty-eight hours. Only in the nine cases, of what might be termed fragmentary constipation, was residue left in the rectum longer than forty-eight hours, and in one case was detected still there a week later.

The Secretory Activity of the Stomach. Was within the range of normality in 1 male and 12 females. Three males and 15 females showed hyperchlorhydria; 1 male and 11 females hypochlorhydria. Of 9 females, whose symptoms at the onset were typical of clinical hyperchlorhydria, 4 showed a high acid curve, 3 a normal curve, and 2 a subnormal curve. In all, the stomach symptoms have tended to fall into the background or disappear.

Other Findings: (1) *Cardiovascular.* In none of the cases is the systolic blood-pressure at present above 120 mm. Hg. In 3 males and 10 females it lies between 100–120 mm. Hg, and in 2 males and 26 females it is under 100 mm. Hg. If we assume the average pulse-pressure in health to be 40 mm. Hg, the most constant finding in all these cases is a pulse-pressure which never exceeded 30, and usually lies somewhere in the neighbourhood of 20. The lowest pulse-pressures are found in those who complain much of feelings of faintness and sinking in the epigastrium.

(2) *Genito-urinary.* The right kidney is palpable in 2 men and 15 women, and both are palpable in 7 females. In none is the left kidney alone palpable. In the severe cases, all unmarried females, the genital organs show some degree of infantilism.

(3) *Integumentary.* Pigmentation of the skin, upon which Lane lays so much stress as a symptom of chronic intestinal stasis, was absent in all the worst cases. On the other hand the most severe degree of pigmentation, almost amounting to that met with in Addison's disease, is to be observed in 2 women whose general symptoms and degree of constipation are the mildest in the series. What is present in all the severe cases is a complexion which might be likened

to a very dirty chalk white.   In none is hyperidrosis prominent or troublesome. The most interesting skin lesion common to these cases is a special form of paronychia which develops independently of trauma or obvious infection.   It is of a chronic relapsing type as a rule, with a painful red swelling of the tissues around the nails, rarely going on to pus formation.   The nail has an eroded appearance suggestive of ringworm, but microscopic examination has been always negative.   In two cases all the fingers were affected.   More usually only one or two on each hand show the condition, which occurred in 32 others; 15 of these belonged to Group II.   In two, in which only one finger was affected, I removed the nail in the hope of preventing its further development but without success; a finger on the other hand was attacked several months later.   Local treatment seems of little avail since the condition tends to disappear with the individual's general improvement and to recur with a relapse in the general condition irrespective of the treatment adopted.   In severe cases the fingers never become completely healed, but in the less severe they appear quite normal in the intervals between attacks.

(4) *Other Systems.*   Enlargement of the thyroid is to be seen in 5 women. Metatarsalgia was present at one time or other in no less than 30 of the women and in the 2 asthenic males; in all it was relieved by suitable supports after the failure of exercises.

Group II.   I now pass on to consider the second group of 15 males and 96 females seen by me when their symptoms first compelled them to seek advice. Instead of analysing this group on similar lines to Group I, I propose to review these patients as a problem in diagnosis, and finally to utilize both groups for some remarks on the genesis, evolution, and treatment of the condition.

Since most writers on the subject of chronic intestinal invalidism deal with the condition as if it originated not before adult life some explanation is desirable why children are included in my figures.   In a previous section the suggestion was made that there is a certain amount of evidence for regarding the chronic digestive disturbances of infancy, childhood, and adult life as different age-manifestations of a common underlying cause.   By tabulating the symptoms in the order of frequency with which they present themselves before puberty, and by similarly dealing with them as they appear after puberty, further support is obtained for this suggestion.

| Before Puberty. | | After Puberty. | |
| 34 Cases below 14 years of age. | | 77 Cases above 14 years. | |
9 males, 25 females.	%	6 males, 71 females.	%
Wasting	90	Constipation	85
Loss of appetite	90	Abdominal discomfort	75
Colicky pains in the abdomen	85	Flatulence	75
Nervous symptoms (irritability, sleeplessness, night terrors)	75	Loss of energy	70
		Wasting (loss of weight)	40
Attacks of pallor	66	Headache	35
Loss of energy	60	Insomnia and depression	25
Constipation	33	Nausea	15
Vomiting	10	Loss of appetite	12

If we tabulate the commonest associated signs we find :—

Before Puberty.	%
Excess of mucus in the stools . .	98
Sallow ('Pasty') complexion with dark rings round eyes	90
Puffiness under eyes	90
Distended abdomen	75
Amyotonia	70
Furred tongue	50
Cold extremities	35

After Puberty.	%
Sallow complexion ('pasty') . .	70
Cold extremities	65
Furred tongue	60
Tender abdomen	52
Offensive breath	30
Amyotonia	25
Distended abdomen	10

It is at once obvious that there is a striking similarity. The symptoms and physical signs are identical for both, and only differ in their incidence per cent. This seems to be due chiefly to the metabolic differences between the child and adult and to the absence of auto-suggestion in the former. Since childhood is a period of rapid growth any interference with the utilization of food material is at once reflected in the weight curve. Moreover, the greater instability of the nervous and vasomotor systems of the child make them more responsive to even slight disturbances in the body economy. On the other hand we see the ready auto-suggestibility of the adult reflecting itself in the prominence given to constipation and abdominal pain, both of which are associated in the lay mind with grave consequences. Also the greater variations in the adult's experience of life tend to make symptoms somewhat different from one case to another, whereas in the child they tend to run true to type from one individual to another.

A striking difference between the children and the adults is the very high incidence of mucus in the stools of the former. In the child a stool which shows no gross particles of membrane, if shaken up in water and the liquefied faecal material drawn off, will be found to have had a large quantity of mucus present. Yet I have never seen a typical attack of muco-membranous colitis in a child. The colicky pains in children may be accompanied by little or no mucus in the stools, or the pains may be absent when the mucus is abundant. In the adult, on the other hand, it is only after other symptoms have been present for a considerable length of time that mucus begins to appear. This is generally present in excess for several months before typical attacks of colitis occur. Only 5 cases in my second group had attacks, and in 2 they were the first symptoms to appear. In the other 3 they developed notwithstanding the fact that the patients were under treatment at the time, and in all they were very definitely dependent upon emotional influences. Little need be said of the physical findings since these were chiefly negative.

In the relationship between habitus and symptoms certain differences were noted in the cases before and after puberty. In the cases before puberty Seaham's findings were corroborated, in that these children were all on an average 2 in. taller, 5 in. less chest circumference, and 4 lb. under weight, compared with a normal child of the same age. No such uniformity was discovered in the adult group.

Of the 77 adults only 10 were of the definite asthenic habitus; 15 were definitely taller than the average height; 15 were of a definite pyknic habitus; while the remaining 37 in no way differed from the average standard. As regards blood-pressure, this tended to be uniformly below the average for the age in each child in the cases before puberty. In the adults, in 2 males and in 10 females with an early menopause, hypertension was present; 4 males and 40 females had pressures within normal limits for the age period, while the remainder showed hypotension. Palpable kidney was present on the right side in 3 children of the ages 11, 12, and 12½ years, and in 10 of the women. In 3 women the kidney was palpable on both sides. It was palpable in only 1 adult male, and on the right side. The secretory curve of the stomach was determined in 2 males and 8 females, all adults, chiefly for the satisfaction of the patients. In none did the curve exceed the normal limits.

Diagnosis.

When after most careful physical examination, repeated at intervals with the assistance of laboratory and radiological methods when necessary, the findings remain negative, the diagnosis suggests itself. Yet there tends to linger in the mind of the physician a doubt that after all some underlying organic condition may have been missed, an occult tuberculosis, or a neoplasm, &c. This doubt serves a useful function if it ensures an attitude of vigilance to detect early any lesion which requires specific treatment, medical or surgical. But nothing is more fatal to the interests of the patient than to betray, by manner or speech, this state of mind. Having reasonably satisfied himself of the absence of organic disease, the physician should proceed to base his diagnosis in each case on a consideration of the interplay of three factors—the medical, the social, and the mental.

The medical factor will have been already partially disposed of in the routine physical examination. In many of these cases medical abnormalities are to be discovered of trifling significance in themselves. When these produce a reaction out of all proportion to their importance they afford a suggestive clue to the kind of individual with whom one is dealing. Early flat foot, hypertrophic rhinitis, and occipital fibrositis may be taken as examples of what is meant. Symptoms connected with them may so dominate the clinical picture that it is only when they are relieved that the underlying general malfunction becomes evident.

Far greater in importance is an investigation of the social factor. Even in the child this factor is not an unimportant one. Severe cases of chronic intestinal indigestion are rarely met with in the homes of intelligent parents. They almost invariably develop in the environment of faddy, over-anxious, and semi-invalid mothers, where only too often faulty food adjustment, faulty mental adjustment, and active suggestion of ill-health are conspiring together against the healthy development of the child. These factors have to be investigated in their bearing on the symptoms presented by each individual case. In the adult the most important

social factor is that of the ' square peg in the round hole '. It may be that the individual's work is excessive for his particular constitution, that by monotony, by the responsibility it entails, and so on, it is making demands that cannot be met. Defective parental and marital adjustment may be adding their quota towards the production of symptoms. Some carefully-guarded secret, the nucleus of a state of fear or conscience, may require careful probing before its etiological significance becomes manifest. Not until the social factor has been carefully explored can all its ramifications into the mental and physical life of the patient be even guessed.

Perhaps of greatest diagnostic importance is the patient's type of mental make-up. The most characteristic finding is a constant over-reaction to stimuli of all kinds. In children it displays itself in fretfulness, easily disturbed sleep, night terrors, readiness to weep on the slightest provocation, inability to keep still, incoordination of movements and habit spasms. In the adult we may find inability to concentrate, capricious appetite, disturbed sleep, nightmares, over-responsiveness to joys and sorrows, excessive sensitiveness to imagined harshness and insult. The assumption of fictitious cheerfulness often displayed by these patients while they are describing their attacks of palpitation, praecordial pain, abdominal discomforts, and so on, tend to throw the casual observer off the track but is very suggestive to one who is persistent enough to penetrate below the surface. More generally, however, they describe their symptoms in excessive detail, and emphasize the intensity of their sufferings by the use of such expressions as ' agonizing ' and ' intolerable '. This is accompanied by a characteristic querulous note in voice and manner. Finally, the medical history of the individual, literally from the cradle, requires to be carefully reviewed for its prognostic as well as its diagnostic import.

The earlier malfunction manifests itself, and the more frequently the symptomatic attacks occur the less likely is the patient to succeed in satisfactorily adjusting his or her life. From the diagnostic point of view such a history reveals better than anything else what kind of an individual one is dealing with, and how he will continue to react mentally and physically to his environment. Similarly, due attention should be paid to the types of stress and strain which appear to determine the onset of symptoms. The result of such an investigation may be illustrated by summarizing the early history of the individuals comprising my first group. In this it was possible to secure independent or confirmatory evidence from outside sources.

Of these, one male and nine females were the youngest of a large family, born near the end of the reproductive life, but of healthy stock with healthy brothers and sisters. Two males and fifteen females were the offspring of ailing parents whose brothers and sisters had died in early life, or who were still alive but in indifferent health. Two males and eleven females were only children whose mother had ' never been the same ' after the patient's birth. Without a single exception, they all had been difficult to rear until past infancy. From five years of age onwards four males and thirty females were said to have shown

'weakness', 'anaemia', or 'threatened consumption'. Circumstantial evidence suggests that the condition described in such phrases was really one of chronic intestinal indigestion. The majority improved in health after the ninth year, by which time they had passed through the gamut of the usual infections of childhood, each of which they had experienced in a severe form. In all the females the onset of puberty was stormy; dysmenorrhoea, irregular menstruation, severe emotional disturbances, difficulties with school work, and insomnia were the rule. After a prolonged puberty, in five cases these symptoms gradually passed away, and a period of several years elapsed before the development of intestinal ones occurred. In twenty-two the puberty symptoms continued, with some improvement, until marriage, when they were gradually replaced by the intestinal ones. In eight, which includes all the individuals of pronounced asthenic habitus, intestinal symptoms appeared along with those of puberty, and there rapidly developed an intestinal invalidism which has lasted ever since. The influence of marriage revealed itself as follows: The only married male suffered from 'dilated stomach' after getting engaged, and this necessitated a postponement of his marriage. Another attack occurred after marriage, and now a third, a somewhat severe one, has followed upon the birth of his first child. He is never 'really well' in the intervals. Of the women, four are single, ten married with no children, seventeen with one child and five with two or more children. Four of them were 'not strong' when they married; six commenced to ail in the first year of marriage. The seventeen with one child all state they have 'never felt the same' since the birth. Of the five who have had more than one child, four started symptoms in a mild form after the second child. These got worse with each subsequent pregnancy but never reached the severe or persistent type met with in the other cases. If there was anything in the theory that repeated pregnancies, by weakening the abdominal wall and bringing about a dropping of the viscera, are a causal factor in the production of this condition, these five cases should be the severest in the series instead of the mildest. Moreover, examination of an unselected number of healthy middle-aged multipara from an industrial population strongly negatives this view. Many of these will be found leading healthy, strenuous lives, notwithstanding tissue-like abdominal walls, with a retracted epigastrium and a bulging hypogastrium. This seems sure proof of what little importance the abdominal musculature and the position of the viscera, *per se*, play in the genesis of symptoms.

The thin, flaccid wall of these healthy women lends itself to easy palpation of the abdomen. The toneless abdominal wall of the chronic intestinal invalid, on the other hand, frequently makes examination very difficult on account of its readiness to fly into spasm from the slightest stimulus.

Of the eight whose symptoms had followed on from the disturbances of puberty, two had been in constant conflict with a mother-in-law, four had experienced a prolonged struggle between an intensely emotional nature and sexual ignorance, while two had been in conflict with an imperious father.

Of the ten with no children four had an intense fear of pregnancy, four had married in sexual ignorance and were anaesthetic, and two had unsatisfactory husbands. Of the seventeen with one child fifteen had had a long and difficult labour and dreaded becoming pregnant a second time. In the other two labour had been easy, but a prolonged period of strain had followed in nursing a marasmic infant. Of the five multiparae the number of children were respectively 5, 3, 6, 4, 4 ; and it was only after the birth of the last child that symptoms became sufficiently pronounced to compel the patients to seek medical advice.

Varied factors appeared to determine the onset of symptoms at this time ; fear of more children, the children becoming 'more trying' as they grew up, fear of losing their husbands' affection and such like seemed to be common factors.

Of the two types of mental reaction which may be displayed by the intestinal invalid, the fictitiously cheerful and the querulous introspective, two single men and six married women were of the former type, while all the remainder were of the latter. Five women of the 'cheerful' group were of a very severe type, and one had only to observe them from week to week to realize how much useful work they had performed in spite of their invalidism.

Yet it was obvious they differed from the normal in several respects, particularly in possessing a most exaggerated sense of duty. They are of the type referred to by Allbutt (9) as self-effacing, uncomplaining, and of such high ideals that they are for ever lamenting, with a wan smile, that their symptoms prevent them from doing all they would like to be able to do in the service of others. Of the querulous introspective type, all had apparently possessed a strong egoism which early found itself in violent conflict with a physical deficiency plus an overpowering environment. A certain few of these patients find an adjustment between their ego demands and their ineffectiveness as long as they are shielded from any excess of environmental pressure. The majority, however, succumb to the slightest pressure, and instead of being able to make any adjustment they seek refuge behind their symptoms, and obtain by sympathy the power and dominance denied them by their own ineffectivity.

I do not propose to discuss the differential diagnosis of this condition from the well-established organic disorders. This is considered fully in all the standard text-books, and I have little to add from my own observations. There is no reason why an organic condition should not develop in the chronic intestinal invalid, and it is often difficult to make certain that a patient in the early days of observation has not an organic lesion. Yet in all the years these forty-one cases have been under observation no organic lesion has ever been detected. My own observations agree with the teaching of the Leeds School of Surgery, which stresses the importance of the clinical history. This, along with a careful general clinical examination, is probably of greater value than all the other methods of investigation so far devised. The present position of chronic appendicitis has been already discussed. As regards the gall bladder, it is

possible not only to make certain of the presence or absence of stones by radiology, but even to determine its functional integrity by cholecystography. In fact the very success of the latter method has already led to meddlesome surgery.   Martin (420), Muller (475), and others, dissatisfied with the results of removal of the non-calculous gall bladder for the cure of vague gastro-intestinal symptoms, find the evidence far from conclusive that 'a very slight infiltration of the gall bladder wall and a lipoid deposit in the mucosa can cause acid indigestion, a feeling of fullness in the epigastrium, flatulence, and intermittent pain'.   As regards the mimicry of duodenal symptoms Irving Gray (246), from an analysis of 250 cases of suspected duodenal ulcer, found that 41 per cent. were due to tobacco smoking, 23 per cent. to chronic gall bladder disease, 18·2 per cent. to constitutional inferiority, and 17·8 per cent. to a variety of conditions; these figures justify one in hesitating before labelling every case of delayed pain after food as a case of peptic ulcer.

One wonders how many of these cases of chronic gall bladder disease were of the type already referred to in which surgical interference failed to remove the symptoms.   There is only one manifestation of chronic intestinal invalidism which may make the physician hesitate to wait, and that is where an exacerbation of symptoms closely resembles an attack of acute appendicitis.   Even in such a case a normal or subnormal leucocyte count should fortify the surgeon in withholding his hand.   Needless to say, I exclude the overwhelming toxic case with a leucopoenia.   Here the patient is so obviously ill with an intra-abdominal catastrophe that the course of action is at once obvious without embarking upon the refinements of a differential diagnosis.

Finally, the late results of surgery in these cases may be briefly summarized. Of my forty-one cases none of the males underwent any surgical procedure. Amongst the females the following procedures had been tried in twenty-five before they came under my observation.

Appendectomy, 25.   Of these, twenty stated they were no better for the operation, four were improved, and one decidedly worse.

Caeco-colon Fixation, 16.   All were improved for six months to a year, after which the symptoms returned worse than before.

Hemicolectomy, 10.   Of these, two very much improved, seven no different, and one worse; in all the constipation persisted.

Gastropexy, 4.   All these stated a marked improvement was noted for about nine months.   Then, in all, the symptoms returned worse than before.

Uterus Fixation, 2.   *Kidney Fixation*, 3.   *Gastro-enterostomy*, 3.   All without any improvement.

Three cases had each an appendectomy, a hemicolectomy, and finally a gastropexy performed without relief.   The caeco-colon fixations were done after a previous appendectomy in seven.   The present state of the twenty-five who underwent some form of surgical interference is to-day very much worse than that of those who escaped it, although the notes suggest that the latter's symptoms were just as disabling in the early stages as those of the former.

These figures corroborate the impression already obtained from a study of the literature, namely, that nothing is more disastrous than surgical intervention in the chronic intestinal invalid. As a method of treatment it is useless; as a method of diagnosis it is criminal.

Treatment. My remarks will be confined chiefly to the treatment of the condition in the adult. Chronic indigestion of the child is adequately dealt with in all the standard text-books with a uniformity unusual in medicine, and will be touched upon here only in a few of its aspects.

The first step in the treatment of the chronic intestinal invalid is to secure the confidence of the patient by a thorough, but not excessive, general medical examination. Hutchison (309) is right in stressing the harm done to these patients by the modern 'clinical team' method of investigation. When the clinical findings turn out to be negative the greatest care, tact, and sympathy are required in explaining to the patient how genuine distress and real ill-health may exist in the absence of a definite disease. If the meaning of a negative finding is not explained tactfully to these sensitive individuals they immediately suspect that the physician thinks there is nothing the matter with them, and at once a barrier is raised which prevents any further investigation of their mentality. Suitable to the intelligence of the patient, analogies from everyday life may be employed to show how a disturbance in function may often produce far more serious disablement than a change in structure. This will naturally lead to an explanation of how changes in body functions may be brought about.

The influences of heredity, constitution, environment, &c., may be lightly touched upon as a preliminary to investigating the life-history of the individual. From the latter may be selected facts which suitably illustrate the explanations already given. If this is done the patient is in a better position to appreciate the rationale of the treatment suggested and to co-operate intelligently. A certain degree of dogmatism is necessary, but the physician should make it clear that, while he is perfectly convinced of his findings at the moment, neither he nor anyone else can be equally dogmatic about the future, and that, should new symptoms appear or the old ones persist, further examination will undoubtedly show what is wrong. In the treatment of an individual case the chief objective is to increase the resistance to fatigue. Success will depend upon how far the patient is constitutionally capable of developing an increase in resistance, how far the social environmental stresses may be altered, how far the mental reactions can be modified, and whether or not the gastro-intestinal tract is capable of responding to direct specific treatment. These four factors are so intimately interwoven that failure with one and success with another do not mathematically balance, and the net result may fall far short of the object desired. Unfortunately, from circumstances entirely outside the control of the patient or the physician, one or other of these factors may be irremediable, and it is precisely for this reason that this class of patient is so frequently the despair of clinical medicine. These factors may now be considered seriatim.

(a) *The Constitutional Factor.* If constitution represents the up-to-the-

instant result of environment acting upon inherited factors, it is of necessity beyond our control, since we cannot alter the inherited potentialities. Yet since these potentialities frequently express themselves by reactions which achieve the dignity of pathological states, successful treatment of these states must of necessity lessen the total burden which these patients have to carry. In other words, general clinical examination may reveal conditions of little importance in themselves, and of no direct etiological significance in the production of gastro-intestinal symptoms, yet of profound significance for the patient as a whole. The summation of stimuli arising from a series of such conditions may so lower the threshold of sensibility that the slightest degree of gastro-intestinal malfunction becomes intolerable. Obviously, then, our first duty is to correct to the best of our ability all such conditions that we find. But a word of caution may be uttered here against excessive or meddlesome therapeutics. Removal of teeth or tonsils that are not clearly and definitely septic, attempting the impossibility of sterilizing the cervix uteri, and similar measures are to be severely deprecated. Abnormal modes of reaction like asthma, paroxysmal rhinorrhoea, vasomotor disturbances, are best left without direct treatment. In these cases the attacks tend to lessen, *pari passu*, with the general improvement. A certain number of conditions which are commonly found and which do require active treatment may be mentioned.

First and foremost, on account of their direct effect on the abdominal viscera, are anal fissures, and painful tags about the anus. These are often not mentioned by the patient and may require to be searched out. Nothing is more dramatic than the relief of general and intestinal symptoms which frequently follows the cure of an unsuspected anal fissure. Falling of the plantar arch is a very frequent accessory factor in the production of that 'tired and exhausted feeling'. It is obvious that continuously aching feet must induce a lack of energy and inhibit any desire for exertion. Since many of these cases are so exhausted that exercises are out of the question, plantar supports must be worn until the general improvement is sufficient to permit the usual remedial ones. Possibly more commonly than is suspected, some of the abdominal pain and backache complained of may arise from lax sacro-iliac joints. A snugly fitting sacro-iliac belt is certainly of the greatest benefit in some cases. Strangely enough, in my experience scoliosis is an unusual finding in adolescent cases. Far more commonly it occurs, as an isolated phenomenon, in otherwise healthy children. In one case in which it did occur it offered a very difficult problem for treatment since the child was neither able to tolerate a jacket nor persevere with the special exercises devised for it. Pruritus and pruritic skin lesions, so common in women, should receive immediate treatment and, where possible, by a single dose of X-rays. The removal of such a source of irritation often rapidly advances the patient along the lines of general improvement.

Minor degrees of astigmatism should be accurately corrected. Chronic hypertrophic rhinitis, or a deflected septum, if of sufficient degree to obstruct nasal breathing requires treatment to restore the air way. But in patients the

subjects of paroxysmal rhinorrhoea and asthma the less local treatment given to the nose the better. Few, if any, of these patients will not, at some time or other, ask for a tonic. The feeling of exhaustion, tiredness, inability to think, &c., all suggest to the lay mind the necessity of something to 'tone them up'. While of course it is obvious that the harassed mentality requires sedative, and not tonic treatment, there are times when one is tempted to try one or other of the 'tonic' remedies—strychnine, iron, arsenic, &c. In my experience these patients are very intolerant of such drugs. By mouth, they invariably upset the gastro-intestinal tract; hypodermically, they have never appeared to me to do anything but harm since they grievously disappoint the patient who usually expects from them a magic effect which does not materialize.

(2) *Social Factor*. Just as man cannot choose his parents, so he cannot alter his birth environment. Most of these patients have been an only child of an ailing mother or the last born of a large and robust family. In the former case the child, often weakly from birth, has been brought up in an atmosphere of invalidism from which it cannot escape; in the other case the child has invalidism forced upon it by the unwise attention of a mother, over-anxious for the child 'who was the first to give her any trouble'. Labouring under the defects of an inferior constitution, these children grow up impressed with their difference from other children. Surrounded as they are by healthy children they cannot avoid having the feeling of inferiority continuously impressed upon the plastic, suggestible mentality of youth. Each case has to be judged on its own merits, but the physician may often secure, if economic conditions permit, suitable adjustment of these environmental defects, by tact and judicious advice. Later, school conditions require careful consideration. Many of these children are highly intelligent, over-conscientious, and apply themselves intensively to their lessons. They tend to be amongst those who are 'pushed' for the honour of the school, with disastrous results. At the first signs of fatigue lessons should be cut down to a minimum and never allowed in excess of the individual child's ability to deal with them easily and comfortably. They tend to pass through a stormy period at puberty, when all the authority of the physician may be required to assure the parents that, with careful handling, nature will in time readjust itself. The choice of a career probably requires the greatest considera- tion of all. One may say without fear of contradiction that at least 90 per cent. of the cases which break down in adult life do so because they find themselves 'square pegs in round holes'. The remaining 10 per cent. do so because, ardently loving their work, they put more into it than they can possibly con- tinue to supply. Unfortunately, in many cases financial circumstances preclude a change, and often little can be done other than to remove all burdens except those that must be borne. This applies specially to cases where marriage is the career which determines the breakdown. A real love marriage based upon a thorough understanding of sex life is the surest preventative of these serious maladjustments which so frequently express themselves in the most aggravated forms of gastro-intestinal invalidism. For the fortunate few whose financial

circumstances permit it, and where the marriage tie is not a bar, a complete change of occupation, or the following of an occupation in more congenial surroundings, will often contribute largely to the success of other lines of treatment. This may be illustrated by the case of a very clever young woman who was trained for the teaching profession, and who was regarded by her colleagues as likely to be a brilliant success if her health would only permit. For five years she suffered from such indifferent health that she could not teach for longer than a few weeks at a time. After great opposition from her parents and others she was induced to quit teaching and learn afresh secretarial work. For three years now, in her new occupation, she has enjoyed a state of health and well-being she had not known since her childhood days.

(3) *The Psychological Factor.* It is held by many authorities that there is a type of mental reaction peculiar to chronic intestinal invalidism. This is only partly true since no two consecutive cases are likely to present a similar reaction. What is found is that in these cases, no matter what the final reaction be, whether that of hysteria, anxiety, neurosis, &c., there is invariably present an inferiority complex which dates back to childhood. If the child has had ill-health dating from infancy a state of anxiety tends to be engendered in the parents which acts as a constant source of suggestion to the child that he or she is not as other children. This exaggerates and intensifies the natural inferiority which all children must feel in the presence of adults. As these children grow up one of two things may happen. Some accept their inferiority and seek security, peace of mind, and social equilibrium by following the path of least resistance. Even the path of least resistance may produce a strain greater than a very inferior mentality can cope with. In such case no attempt is made to combat it, and refuge is sought in a state of uncomplaining invalidism. This tendency should be looked for in early life and counteracted by advising the parents to employ a little judicious neglect and let the child risk facing many of the things he is being guarded against so carefully. Other children react differently. Unconsciously considering themselves neglected and discriminated against by both Nature and Mankind, they rebel against fate. In childhood this rebellion displays itself by one or other variety of the 'problem child', whose vagaries are so often put down to poisoning from his intestinal tract. The acute infections tend to attack the central nervous system in these children. There is evidence that chorea, for example, develops only in the type here considered.

If they successfully weather these storms of childhood they tend to be unusually bright and intelligent, and undertake tasks at school far beyond their powers. With the violent eruption of puberty temporarily paralysing their activities, every experience becomes interpreted as a defeat; they lose confidence in themselves and unconsciously seek solace in their physical symptoms as being an efficient cause and a satisfactory explanation of their failure. Obviously these children require a very careful grading of their school tasks, and a very efficient preparation for puberty, so that they may not be taken unawares by the

physical and emotional changes they feel so intensely.   Cases seen in adult life usually have acquired one or other of the neurotic reactions which obscures their inferiority complex.   In them the process of repression, which is a normal accompaniment of healthy childhood development, has not succeeded in bringing about the sublimations that characterize mental health and harmony.   Deprived partially of this indirect means of gratifying the primary instincts, the individual suffers more than normally from any accumulation of sexual tension that may occur later.   Abrupt introduction to sexual knowledge, often of an erroneous type, may result in undue repression of the mental impulses which are struggling for recognition at puberty.   The various inhibitions thus formed may hinder the ability to experience sexual satisfaction when a suitable opportunity presents itself in marriage.   It is for this reason that so many cases come to grief in the first year of married life.   With most other diseases, this specific agent, i.e. undue repression, may be present in many cases without causing symptoms; it all depends on the intensity or dosage and the degree of adjustment possible for the individual.   When the degree of adjustment is small and the repression is great, the conflict may reveal itself on the physical level by gastro-intestinal malfunction.   This may then react and make manifest a previously latent neurosis.   In severe cases the anxiety neurosis may be so intense as to completely obscure the true nature of the case.   Such cases require a psychological analysis to resolve the neurosis before it is possible to deal with the underlying inferiority complex.   Until the resolution is effected no treatment of the digestive symptoms is likely to be effected.

These are the cases which pass from one medical man to another, always hoping for a relief they never obtain and never can obtain until they have had adequate treatment first for their anxiety.

It must be remembered that the more pronounced infantile types do not desire relief.   Their inhibitions and repressions safeguard them from facing the realities of life, and their physical symptoms safeguard them from any direct attack upon their mental repressions.   In favourable cases, when the true causes of anxiety have been accepted by the patient, attention may then be turned to the adjuvant morbid agents.

It is remarkable what secret fears, worries, and burdens these patients may be labouring under.   Many of these are really insoluble.   It is no use telling a patient not to worry when the cause of it be in some very genuine justifiable but irremediable situation.   It may be profound marital incompatibility, overwhelming liabilities and responsibilities, wastrel children, or many another profoundly disturbing factor beyond the individual's control.   The mental purgation which results from confiding these secret worries to a sympathetic ear often, however, clarifies the muddled mentality and permits a concentration on the main difficulties which was previously impossible when so much mental energy was being consumed by subsidiary and unimportant ones.   Tactfully it should be pointed out to individuals who are handicapped by insoluble difficulties that mental peace can often be secured by acquiescing in things which cannot be

cured. Still more necessary is it that the person, who has started life handi-capped by a defective physique or constitution, should learn the lesson of acquiescence and settle down as best he can with his handicap. For all who are devoting themselves to the fruitless search of a 'cure' that will make them the exact replicas of normal individuals, the motto to guide them aright should be that 'the conquest of Fate is not by struggling against it, nor trying to escape it, but by acquiescence.

(4) *The Medical Factor.* This involves the treatment of the main symptoms and the restoration of the individual to economic efficiency by directly increasing his resistance to fatigue. It is approached through four main channels—rest, exercise, diet, and drugs—the last of which being the least important.

Specific Treatment.

(a) *Rest.* All these cases require some form of rest, but whether it should be rest in bed, rest from work, or simply cutting out extraneous activities can only be decided for each case on its own merits, depending on the severity of the symptoms and the individual's financial circumstances. It is futile to tell a breadwinner to take a holiday if he is to worry the whole time how the family fares on a diminished income, or the individual in a good position which, if once lost, is not likely to be replaced easily. Similarly with an individual for whom these considerations do not count, over-work should not be exchanged for a holiday where the exertions of sport and pleasure add to, rather than diminish, the physical and mental exhaustion. Fortunately in many, by carefully investigating the daily habits of the individual, a little adjustment here and there often results in securing a considerable degree of rest. Early to bed and early to rise secures a restful start for the day's work; where a man or woman can do so, an hour later to business in the morning, an hour earlier away at night, and an hour and a half for lunch instead of three-quarters, means a con-siderable period of rest when spread over several months. A little ingenuity on such lines often succeeds where, at first sight, there seems no possible relief from the wear and tear of the daily round. An essential desideratum in all cases is that they should secure adequate sleep. Since many of them dread having to take a sleeping draught, it is well to point out that the drug they are taking is not a narcotic but something to tone up the nervous system. The idea of a 'tonic' treatment is always more acceptable to the lay mind than a sedative one. Dial or adalin 5–15 gr. is very successful in giving a restful sleep to many. In some, however, the effect only lasts a few hours, and when they awaken they are unable to get off to sleep again. Such cases often do much better with a small dose of bromide after each meal and a final full dose of bromide and chloral at bedtime. As they improve it is easy to drop out the daily bromide, then the chloral, and finally the nightly bromide. If certain individuals find they cannot do without something to take at bedtime, a small dose of bromide can be continued indefinitely without harm.

(b) *Exercise*. It is the fashion at the moment to lay great stress on the therapeutic effect of exercise in these broken-down individuals. The school of Goldthwait in particular promises results almost amounting to the miraculous. While fully realizing the value of graduated exercise, I am impressed by the great harm done to many by the injudicious employment of them at a stage when the patient is not in a fit condition to benefit. In severe cases it is only after a preliminary period of rest that they can be expected to benefit. There is no hard and fast rule to decide when a patient is fit. One can only tentatively try with a very few exercises at a time, always stopping short when producing the slightest feeling of fatigue. In severe cases in which the period of rest is spent in bed, a course of general massage is a useful preliminary. The form of exercise which I have found of most benefit is the simple, time-honoured one, as follows : With the patient on his back, each leg kept firmly extended is raised alternately to the vertical, then both legs together, and finally the body raised from the hips to the sitting posture with the arms extended by the side, and the legs placed firmly against the floor. Each movement is done once, and increased by one each day short of producing a feeling of fatigue. If this is produced the number of times is dropped by one and continued at this number until the patient no longer feels tired. Along with it a simple breathing exercise is ordered. With hands on hips, head thrown back and chin well down, the patient rises slowly on tiptoes as he takes a deep breath. This position is maintained for a few seconds, then the lungs are slowly emptied as the heels are slowly lowered to the ground. The same rule applies to the number of times it is repeated. The patient is also encouraged to try and increase the length of time during which the breath is held at the end of full inspiration.

Wheatley and Moore (464), dealing with the effect of special exercises on children of poor posture and physique but without symptoms, find that in severe cases no real improvement may be expected under two years, and that in really severe cases actual regression may occur instead of improvement. In individuals with symptoms it is obvious that exercises where indicated must be continued over a very long period before improvement is to be expected. A question which continually arises in these cases is whether they should be fitted or not with an abdominal belt, of which there are such a large variety on the market. These date from the period when it was assumed that the patient's symptoms arose from the malposition of the abdominal viscera, and that a properly fitting belt restored them to a normal position. We now know by X-ray examination that even the best fitting belt makes no difference to the position of the viscera. Recently it has been suggested that its efficiency depended upon increasing the intra-abdominal pressure, but my impression is that it very largely works by a process of suggestion and acts more as a mental prop than as an abdominal support. For this reason I have never found it necessary to order one for any individual under twenty-five years of age.

In young adults graduated exercises develop general muscular tone sufficient to keep them comfortable. In cases which have drifted on past twenty-five,

or have developed after that age, I find the neuro-muscular apparatus as a rule fails to recover its full efficiency by exercises alone. Some of these cases may be completely relieved of all other symptoms except one, namely, a feeling of weakness and sinking in the hypogastrium. In them a snugly fitting belt, by removing the last of their abnormal sensations, completes a symptomatic cure which would be impossible to achieve without it.

(c) *Diet*. Dietetic faddism has been ever prevalent in medical as in lay circles. The present age is no exception. Before the days of metabolic research empiricism declared this article of food to be good and that to be bad. In recent times the experimental findings of the laboratory have been carried boldly over into the realm of clinical medicine, and the results in the animal uncritically applied to the human subject. The consequence is that, whereas we find fairly general agreement amongst physiologists regarding their experimental findings, we find nothing but controversy amongst clinicians. If this be the state of affairs regarding the natural food of man in health, how much more so is it the case in the therapeutic adjustment of diet. The Salisbury diet, sour milk, *B. acidophilous* have had their day, to be replaced for the moment by roughage and vitamins. It seems to be forgotten that man has attained his present supremacy in the animal kingdom with an alimentary tract which has successfully handled and maintained health on a greater variety of foodstuffs than any other animal. His ability to do so should be regarded as a function of health, and our aim in the treatment of these cases should be as far as possible to restore this efficiency. The patient when first seen usually has already made attempts to adjust his diet since as a rule, with the onset of symptoms, he found that some article or other did not agree with him. After omitting the article, symptoms abated for a short time, only to return; then another article was incriminated, omitted, and the same result followed. In severe cases the individual may have attained even an actual starvation diet before seeking advice. On the other hand, he may have adopted one of the prevailing fashions and have been filling an irritable colon with residue from fresh fruit, raw vegetable, and bran bread, and wondering why he felt more miserable than ever.

It should be pointed out to the patient that whereas a healthy man may thrive on a wide variety of foodstuffs, others, of which he may be one, have a very reduced capacity in this respect, and that health is to be attained, not by adopting this or that theoretically perfect diet, but by a process of trial and error, always remembering that one man's meat is another man's poison. Stress is then laid upon the simple essentials which are necessary for healthy digestion in all individuals. Sufficient teeth and efficient mastication, adequate time for each meal, with, if possible, a period of rest before and after each. The avoidance of a heavy meal when tired and fatigued, of working long periods without food and the necessity of regular hours, must be insisted upon.

Some simple explanation is then given why a definite diet is being prescribed. It should be stressed that the diet prescribed is not to be a permanent one, but will be continued only until the gastro-intestinal tract has returned to

normal, and that this will certainly happen if easily fermentable foodstuffs and articles which leave a coarse irritating residue are avoided temporarily. A suggested menu is as follows:

Breakfast. Porridge from Robinson's groats, farina, Force, chocolate or cocoa, eggs (poached or lightly boiled only), ham, bacon, rusks, dry crisp toast, ryevita, butter.

Lunch and *Dinner.* Clear and cream soups, any meat, fish, chicken, or game, except duck, veal, pork, crab, lobster, and oysters.

No made-up, smoked or seasoned meat &c. Rice, potatoes, macaroni, spaghetti, spinach, asparagus tips or any other vegetable that can be puréed. No vegetable to be taken which cannot be completely freed from fibres before serving. Starchy vegetables to be taken in great moderation. Simple puddings, custards, sponges may be taken; also plain cake and cream cheese. Fruit juice.

The essential point is that the patient does not eat coarse foods with fibre, skins, seeds, or gristle. He must not eat salads, celery, tomatoes, cucumber, pineapple, nor most of the green vegetables, nor any raw fruit, nor such things as raisins, nuts, and jams full of seeds. At the same time sugar and starch is cut down to a minimum to lessen fermentation.

Seasoning and condiments must be forbidden and the patient encouraged to take meat, fish, and game in the simplest form.

As regards the intake of fluid, this should not be forced, and thirst alone should guide the quantity taken. Smoking and alcohol are forbidden.

As soon as the patient feels quite comfortable, he should be encouraged to experiment by adding one article at a time of the previously forbidden goods with the view to testing the ability of his intestinal tract to deal with it. In mild cases, in time, an ordinary diet may be attained. In severe cases, this is not possible. It should be pointed out to such patients that they are not as other people, that they cannot tolerate an ordinary mixed diet, and that they must accept this state of affairs and keep within the dietetic limits which keeps them comfortable.

Fortunately all these cases stand fats well, so that the body-weight is easily maintained by extra cream, butter, &c., and those who cannot tolerate fresh fruit may take strained fruit juice.

(*d*) *Drugs.* Constipation, which is such a terror to these patients, may require some assistance from drugs, although in the majority of cases the best preliminary treatment is a cessation from the excessive purgation they have been indulging in. A suitable smooth diet in mild cases is sufficient in itself to cure the constipation. In severer cases it is my custom to prescribe liquid paraffin two ounces a day in divided doses until it begins to ooze from the anus and then to reduce it daily until it has ceased oozing. This dose is then continued for a period of three months before any attempt is made to reduce it further. In some cases the liquid paraffin simply oozes away without helping defaecation in the slightest. For these an infusion of senna made fresh daily

by soaking the pods in cold water for twelve hours is prescribed in addition to the maximum dose of paraffin that does not ooze. Each patient has to find out for himself the number of pods which will secure a natural action without pain or discomfort. Before starting it is essential to see that the colon and rectum is cleared out by a simple enema. In many old-standing cases seen late in the stage of chronic invalidism, the enema habit may have become a permanency. Every effort to break them off it frequently results only in great mental and physical distress, and in such cases the only alternative left is to allow them to continue.

The only other drugs permitted to these patients is an alkaline carminative mixture of sod. bicarb. and mag. carb. levis with aromatics to relieve their flatulence. To it may be added in suitable cases a small dose of atropine which is especially valuable where spasticity is a marked feature of the constipation. Even this should be dropped the moment the patient begins to feel comfortable on the prescribed diet. In others a small dose of sod. salicyl appears to act better than the atropine. A certain number cannot tolerate carminatives, and nothing suits them better than a small dose of Sippy's powder after each meal.

If patients presenting the abdominal manifestations of constitutional inadequacy were recognized for what they are, and treated on the broad lines here suggested, I believe the majority would be prevented from drifting into the severer degrees of chronic intestinal invalidism. Not all, for the reason that the severer degrees are accompanied by a psychic inferiority which prevents any co-operation with the physician in accepting facts as they are and attempting any adjustment to them.

This conclusion is based upon the following figures, which show the results of treatment in the cases here reported. ' Cured ' represents cases restored to full economic efficiency ; ' improved ' those comfortable as long as they continue on the lines of adjustment ; ' relieved ' those comfortable but liable to relapse from time to time.

Group I. 41 Cases.	Males.	Females.
Cured	Nil	Nil
Improved	3	4
Relieved	2	12
Not relieved	—	20

Group II. 111 Cases.	Males.	Females.
Cured	12	48
Improved	3	25
Relieved	—	13
Not relieved	—	10

In Group I the twenty unrelieved and five of the relieved had all some form of surgical interference.

In Group II the ten unrelieved represents the type of patient who is incapable of co-operating. The thirteen relieved, on the other hand, are cases who co-operate to the best of their ability, but whose inadequacy is so great that little can be expected from any line of treatment.

The theory of chronic intestinal invalidism here advanced may be unsatisfactory in several of its aspects.   Nevertheless, the recognition of the fact that its treatment should be essentially preventive would do much to reduce the large amount of vague ill-health which exists amongst the general population at the present day.   This is not to be obtained by applying the results of any one special line of investigation, but by the judicious selection and application of all which have a bearing, no matter how remote, on individual well-being.   In this the general practitioner should play the most important role, since he alone possesses the key to that very real entity, the patient's constitution.

Conclusions.

In our present state of knowledge it would seem legitimate to draw the following conclusions from this review of visceroptosis and allied conditions in their relation to chronic invalidism :—

1. The position of the viscera within the abdomen may vary to a considerable extent and yet be well within the range of normality.

2. There is no necessary relationship between the body build of the individual and the position of the abdominal viscera beyond that imposed by mechanical necessity.   That is to say, *ceteris paribus*, the organs will be higher in a short broad abdomen than they will in a long narrow one.

3. There is a considerable range of movement of the hollow viscera which is normal for any given individual, so that their actual position in health may vary from time to time.

4. This variation in position may be brought about, either by physiological factors or by psychical ones.

5. The position of the viscera, *per se*, plays no part in the production of symptoms.   It only does so in rare cases when associated with a true abnormality, as for instance an aberrant renal artery.

6. While one or several of the symptoms discussed may appear as transient phenomena in any individual, their persistence is only met with in those of a special constitution.

7. This constitution is not associated with a special body build, but rather with a state of nutrition and state of mind.

8. This state of nutrition betrays itself in the tall thin individual by underweight, and in the short broad individual by overweight.   In both it is accompanied by poor muscle tone leading to postural defects.   The state of mind reveals itself by abnormal mental reactions.

9. The association of malnutrition, poor muscle tone, and abnormal mental reactivity is characteristic for this group of cases.

10. This association appears to depend on a congenital, possibly inherited inability of the individual to adapt himself satisfactorily to the various strains and stresses of life.

11. One of the failures of adaptation may be lack of resistance to degrees

of infection and toxaemia which have no effect on normal individuals. This may account for the failure to discover the 'toxin' present in cases of auto-intoxication.

12. When sensations from malfunctioning viscera rise into consciousness in an individual who is the subject of repressions based upon an inferiority complex, these tend to be utilized in the form of symptoms to reinforce the repression. The malfunction may originate peripherally from local causes as improper feeding, &c., or centrally from weakening of inhibition produced by fresh mental conflicts.

13. Later, with the establishment of a vicious circle of malfunction-symptoms-malfunction, actual tissue changes may occur in the affected organs, rendering them incapable of a return to normal function.

14. When this occurs there is little chance of restoring the individual to his or her particular standard of health.

15. The treatment of the condition is essentially preventive.

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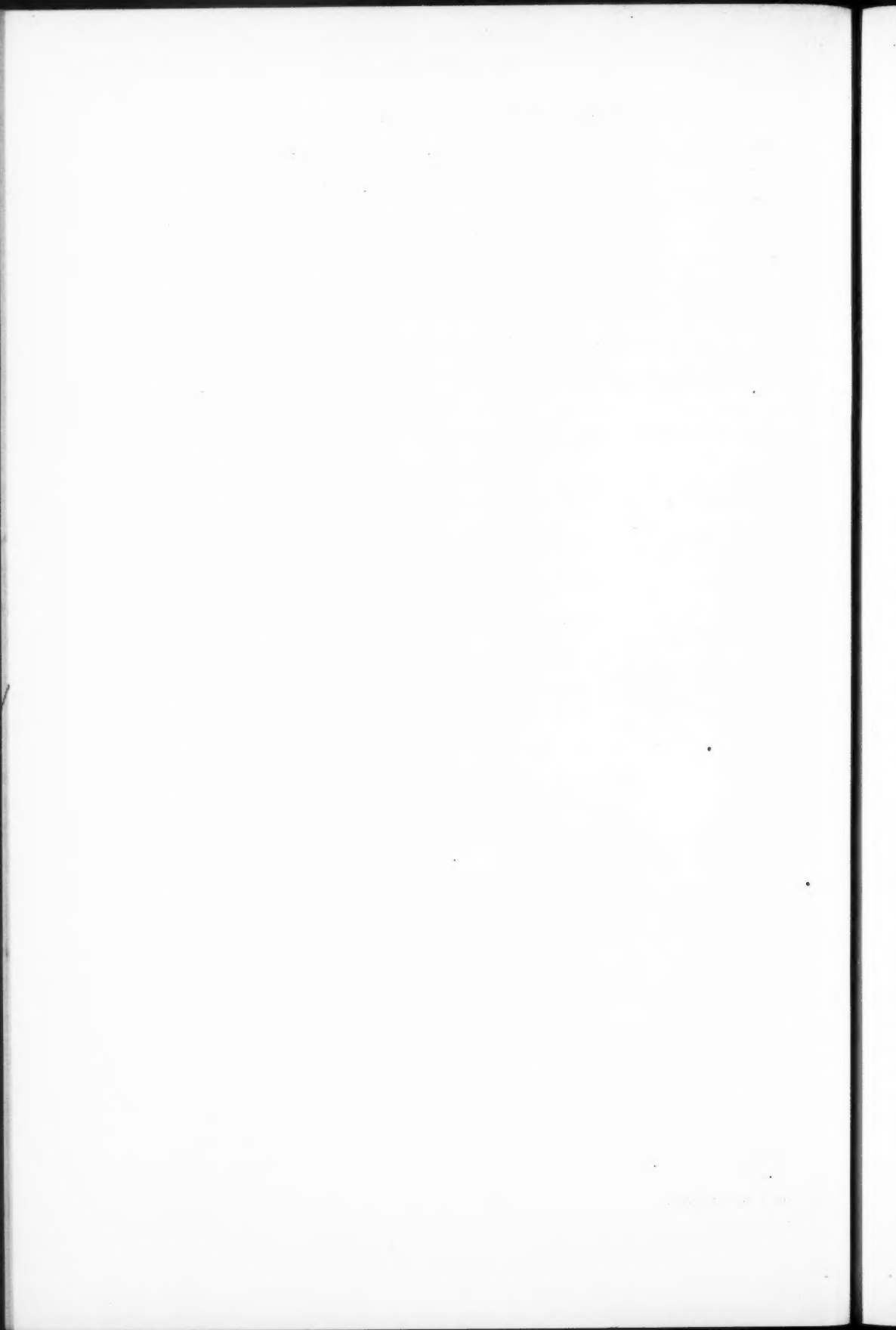
THE ELECTRICAL AXIS OF THE HEART AS AN INDICATOR OF CHANGES IN VENTRICULAR PREDOMINANCE [1]

By H. WALLACE JONES and R. E. ROBERTS

(From the Cardiographic Department of Liverpool Royal Infirmary)

With Plates 1 and 2

FOR many years the subject of hypertrophy of one or other side of the heart is one which has given rise to a considerable amount of thought and discussion. Prior to the introduction of the electrocardiogram reliance had to be placed solely on certain clinical signs as an indication of such hypertrophy. With the introduction of this device into clinical medicine, however, it becan recognized that in the records so obtained one had in many cases a valuab indicator of predominance of one side of the heart over the other.

Lewis (1) has shown that the normal ventricular complex of the cardiogram is made up of two factors, viz. that produced by the left side of the heart or levogram, and that produced by the right side or dextrogram, the fusion of the two producing the normal ventricular complex. If one side predominates over the over, the levogram or the dextrogram will predominate in the record, and so indicate left- or right-sided predominance respectively.

It would be out of the scope of this paper to enter into the question as to what extent hypertrophy of the heart is indicated by ventricular predominance in the electrocardiogram: and though hypertrophy, especially unilateral hypertrophy, does undoubtedly bring about changes in the ventricular predominance as shown in the cardiogram, there are many other factors which must also be taken into account.

Predominance of the right or left side of the heart in the electrocardiogram is roughly indicated by comparing the main deflexion in Leads I and III.

When the main deflexion is downwards in Lead I and upwards in Lead III the indication is that there is predominance of the right side; when upwards in Lead I and downwards in Lead III, that there is predominance of the left side. (The main upward deflexion is as a rule the ' R ' wave, and the main downward deflexion the ' S ' wave, of the cardiogram.)

In order to give a mathematical value to different degrees of predominance, certain formulae have been introduced, such as the White-Bock formulae in America (2) and the one introduced by Lewis in this country (3). These

formulae give a rough indication of changes in predominance. After investigation, however, of a series of cases, it has become apparent that the most sensitive indicator of changes in predominance is the inclination of the electrical axis of the heart.

The simplest and most rapid method of calculating this axis is the Graphic Method introduced by Carter, Richter, and Greene (4). In this the principle of the equilateral triangle is made use of, the three leads of the heart being taken as sides of this triangle. The axis is determined from the electrocardiogram in the following way : The size of the main deflexion upwards and downwards, in millimetres, is taken in each lead, and the smaller deflexion is subtracted from the larger. If the larger deflexion is upwards the number is put on the positive side of zero in the corresponding lead of the chart, while if the larger deflexion is downward, on the negative side of zero ; the number of millimetres on the scale then corresponds to the difference in millimetres between the upward and downward deflexion in that particular lead. A line drawn from the centre of the chart through the point of junction of the lines corresponding to these is carried outwards to the periphery of the chart; the angle between this line (which represents the electrical axis of the heart) and the horizontal can then be read on the scale.

The chart provides for the calculation being done in the I, II, and III leads, but in actual practice it is found that only rarely do the lines exactly cross the same spot in all leads, and it is therefore much simpler to take only two leads, Leads I and III, which as a rule give the clearest indications of changes in predominance of any two leads. The normal position of the axis when calculated in this way is about 55° ; a movement of the axis anti-clockwise indicates a tendency to left-sided predominance, and a movement of the axis clockwise indicates right-sided predominance.

The method of calculating the axis from the electrocardiogram in a normal case is shown in Plate 1, Fig. 1, while Plate 1, Figs. 2 and 3, show the same calculation in cases of right-sided and left-sided predominance respectively.

Group showing the Effect of Respiration and Posture on the Electrical Axis of Normal Hearts.

Respiratory variations in the electrical currents produced by the heart, as estimated by the capillary electrometer, were noted by Samojloff in 1908 (5), before the string galvanometer was in use. Einthoven, Fahr, and de Waart (6), using the string galvanometer, investigated the changes which took place in the electrical axis of the heart as a result of deep respiration, and as a result of changes of posture. They came to the conclusion that these changes were dependent on movement of the anatomical axis of the heart during respiration. They also found that inspiration caused a change in the electrocardiogram in the direction of right-sided predominance, while expiration was found to produce left-sided predominance. Lying on the right side caused right-sided

predominance; lying on the left side, left-sided predominance. These latter findings (i. e. in the lying position) were contrary as regards direction to the later observations of Dieuaide (7), to which we will refer later. Lewis (8), in a case where a rifle bullet had become embedded in the heart, showed that in
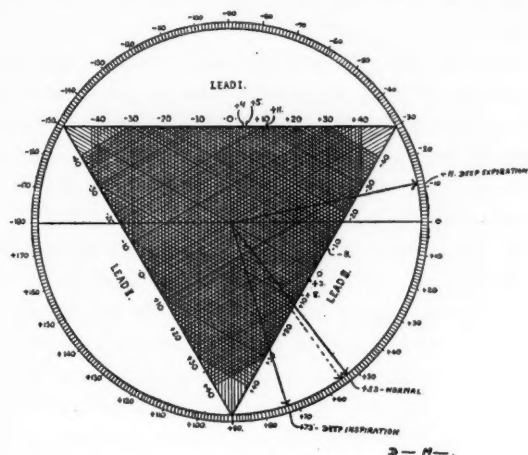
FIG. 4.
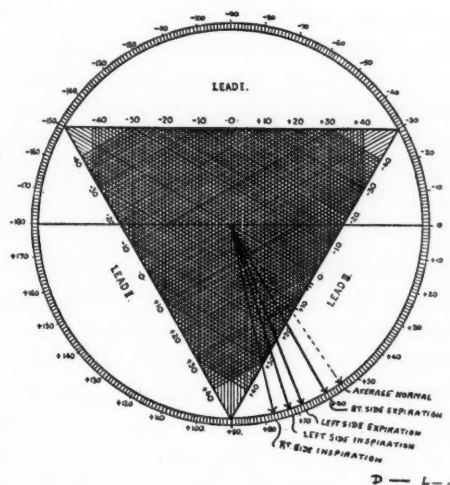
FIG. 5.

the erect position the changes produced by respiration in the anatomical axis and in the electrical axis respectively correspond very closely in direction and degree.

We have recently investigated a series of normal men and women for this change in the ventricular predominance with respiration, using the Graphic Method for the calculation of the electrical axis. The changes which occurred

with deep inspiration and expiration in the standing position were very striking; Fig. 4 is a well-marked example of this, the electrical axis undergoing a rotation of 84° between deep inspiration and expiration. The amount of rotation varies considerably in different individuals. The average amount of rotation was about 40°; the degree of rotation in men was almost universally greater than in women.

When the effect of lying on the left side and the right side alone was investigated it was found that the results were very variable, some subjects showing the type of record obtained by Einthoven, Fahr, and de Waart (6), i. e. right-sided predominance when lying on the right side, and left-sided predominance when lying on the left side, while others showed the reverse condition as described by Dieuaide (7).

We therefore tried the effect of deep inspiration and expiration on the record when in the right- or left-lying position, and found that by far the most important factor in the movement of the axis was the respiratory phase during which the record was taken; the movement of the axis which resulted from rotation from the right to the left lateral position alone was found to be very small. Fig. 5 illustrates this clearly and shows that the only difference between the two positions is that the respiratory movements are more free on the right side than on the left side.

In the cases electrocardiographically examined in different phases of respiration, postero-anterior radiographs were taken in similar respiratory phases, and an effort was made to ascertain if an anatomical or geometrical axis could be found on the X-ray photographs which would correspond in its movements with those of the electrical axis. In spite of the fact that in this endeavour all sorts of possible geometrical axes were investigated no such axis could be found which would correspond in its respiratory variations with those of the electrical axis. This difficulty had previously been encountered by Einthoven, Fahr, and de Waart (6).

Incidentally we quite failed to confirm the observations of von Groedal (9) who, working with an X-ray cinematograph of the heart, came to the conclusion that the heart during respiration revolves evenly round the point of contact of the diaphragm and the right auricle. Our observations tended to show on the other hand that there was, during respiration, no 'fixed' point in the cardiac shadow; that the up and down movement with respiration was very considerable in most of the cases; and that even if this up and down movement was allowed for there did not appear to be any fixed point of rotation.

Fixed Apex Group.

If one examines the movements of the electrical axis with respiration in cases where there is a 'fixed apex beat' clinically, due to adherent pericardium, a marked difference becomes apparent.

Instead of the rotation in direction of the axis with deep inspiration and expiration which one finds with normal subjects, there is in cases of adherent pericardium only an extremely small movement—a striking result which provides, we believe, a very valuable test for this lesion.
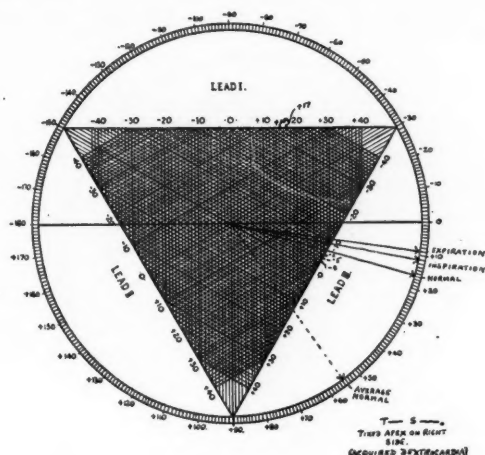
FIG. 6.
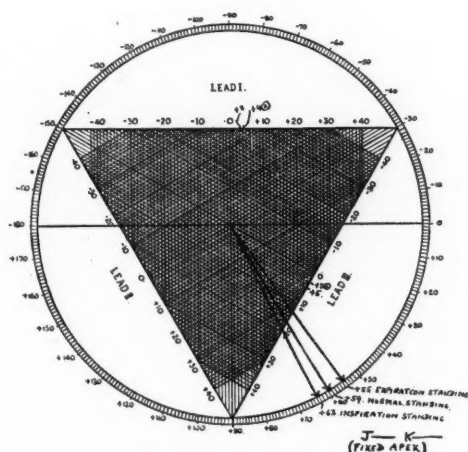
FIG. 7.

Fig. 6 is an example of this change, taken from one of two cases of dextrocardia of the acquired type, in which the apex of the heart has been drawn over to the right side of the chest by pathological changes.

Figs. 7 and 8 are examples of the same change shown in two cases in which the apex beat has been drawn over to the left side and is beating in the axilla. Fig. 9 is a similar example from a case of general mediastino-pericarditis, with general heart failure of the congestive type.

Some years ago Dieuaide (7) advocated comparing the electrocardiogram taken when the patient was lying on the right and left sides respectively as a test for adherent pericardium, and was strongly in favour of this condition being indicated when no change in the predominance could be detected in the two records.
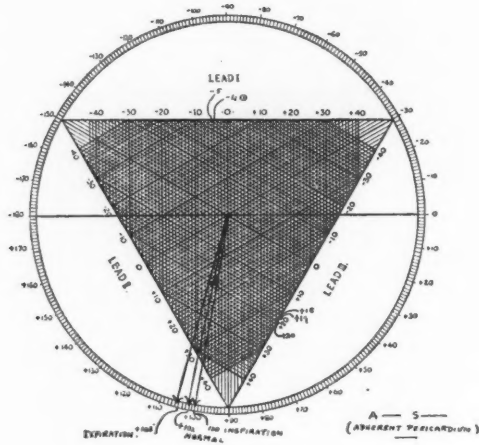
FIG. 8.
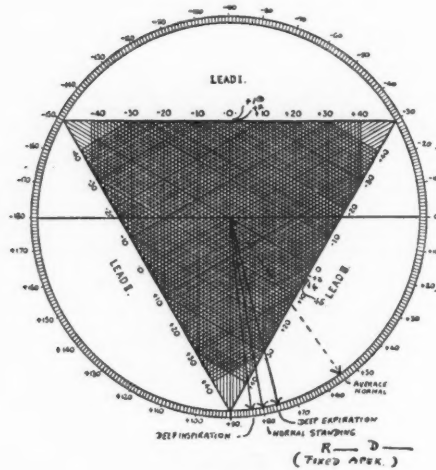
FIG. 9.

In the first group of normal cases it was apparent that even in normal individuals the change which took place between the right and left side positions was small, and we therefore feel that Dieuaide's test is not reliable, and that the test described above, based on the movements with deep inspiration and expiration, is much more definite in its indications; we have found this test to give considerable help in diagnosis.

Transposition Group.

Cases in which there is complete transposition of the viscera show with the electrocardiogram marked evidence of right-sided predominance, in addition to inversion of the 'P' and 'T' waves in Lead I. When the respiratory move-
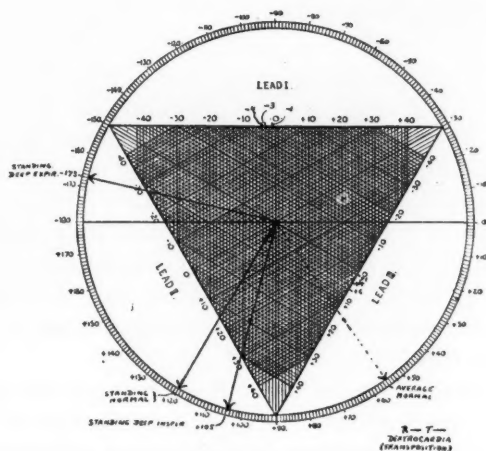
FIG. 10.
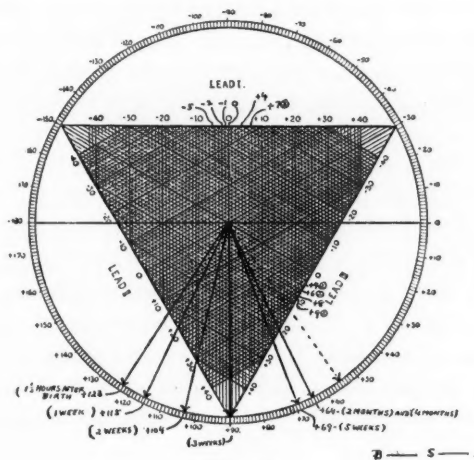
FIG. 11.

ments of this group are examined they are found to be similar to those found in normal individuals, except that rotation is in the opposite direction (i. e. the axis moves anti-clockwise with inspiration and clockwise with expiration), the whole record showing evidence of marked right-side predominance.

Fig. 10 is a typical example of this. If the arm leads are reversed and the right leg substituted for the left, the respiratory movement of the axis becomes

quite normal. The movement of the axis with respiration in this type of dextrocardia is strikingly different from those of the so-called acquired type of dextrocardia where the heart is drawn over to the right side by pathological changes. In this latter group the respiratory movements of the axis are extremely slight or even absent; this fact, along with the inversion of the 'P' and 'T' waves in Lead I of the transposition type, provides an additional means of distinguishing between them.

Baby Group.

The change in the circulation which, at parturition, accompanies the transition from an intra-uterine to an extra-uterine existence is one which has always received considerable attention.

The alteration in the form of the electrocardiogram during the first few weeks of life is also one of extreme interest, for when taken a few hours after birth it shows marked right-sided predominance (3), (10)—the degree of predominance gradually diminishing until the normal position is reached, two or three months after birth.

Children of this age are not easy subjects to record, and it is a matter of some difficulty to get a complete series of electrocardiographs of the same infant taken over the period of transition from right-sided predominance to normal. We have been fortunate in obtaining (Fig. 11) a series of records taken from a normal full-term infant, the first 1½ hours after birth and subsequent ones first at weekly and later at longer intervals until the predominance approximates to the normal. It is shown quite definitely that the greatest change takes place during the first five weeks, and that afterwards the progress becomes much slower.

Plate 2, Fig. 12, is a composite electrocardiogram from the same infant, showing how the changes in predominance appeared in the original series of records. The gradual increase in the size of the 'R' wave and the progressive diminution of the 'S' wave in Lead I are well shown, while incidentally the gradual increase in the size of the 'T' wave is clearly indicated.

A recognition of this right-sided predominance in the first few weeks of life and its return to normal at the end of three months in healthy children is of importance in the early recognition of congenital cardiac disease by persistence, beyond the normal period, of evidence indicating right-sided predominance.

Changes in Ventricular Predominance with Alteration in the Cardiac Rhythm. (A. F. and N. R.)

In this group seventeen cases were examined—some in which the change from auricular fibrillation to normal rhythm was produced by the administration of quinidine, and others in which fibrillation supervened on a normal

rhythm. In ten cases no change in predominance took place with a change in rhythm. Of the remaining seven, all with one exception showed more evidence of right-sided predominance when the heart was fibrillating than when it was beating with a normal rhythm.
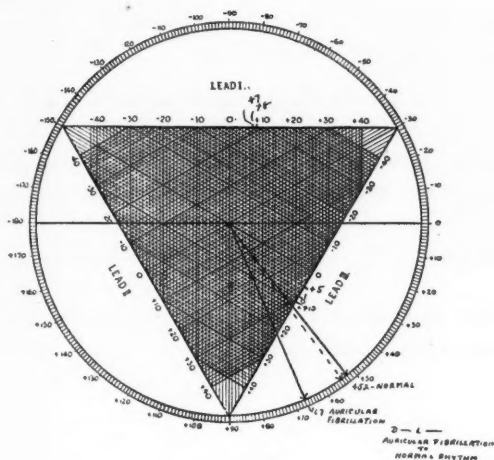
FIG. 13.
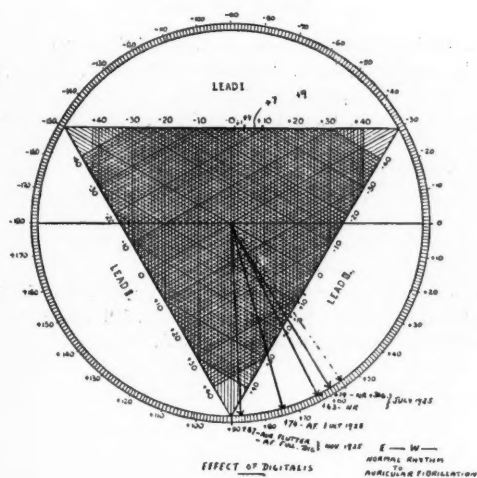
FIG. 14.

Fig. 13 is an example of a change from fibrillation to normal rhythm under quinidine, while Fig. 14 is a record showing the change from normal to fibrillation, with also the effect of digitalis and a transient period of auricular flutter.

This evidence of a tendency to right-sided predominance in auricular fibrillation as compared with a normal rhythm is interesting in view of the case recently described by Reid (11), in which a heart with auricular fibrillation

as its sole abnormality was examined by X-rays, first when fibrillating, and secondly when beating with a normal rhythm. During the fibrillation there was dilatation of the right side of the heart, which disappeared with normal rhythm.

Conclusions.

1. The calculation of the electrical axis of the heart can be determined very quickly by the Graphic Method.

2. It gives a very sensitive indicator of changes in ventricular preponderance—for example, those occurring during respiration and during the early weeks of life.

3. It forms part of a very useful test for adherent pericardium.

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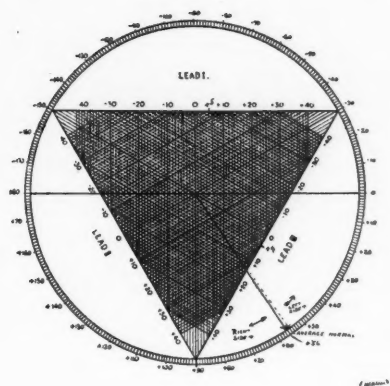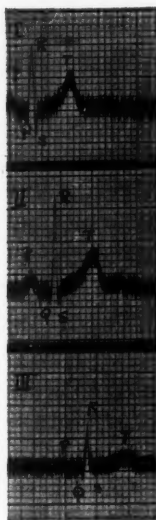
Fig. 1.   Lead I $= +8-3 = +5$
    „   III $= +5-1 = +4$
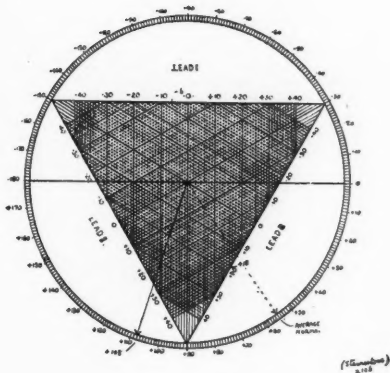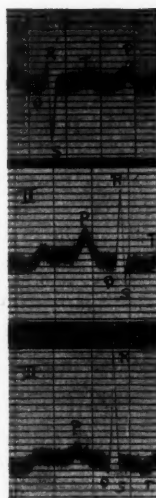
Fig. 2.   Lead I $= +2-8 = -6$
    „   III $= 0+18 = +18$
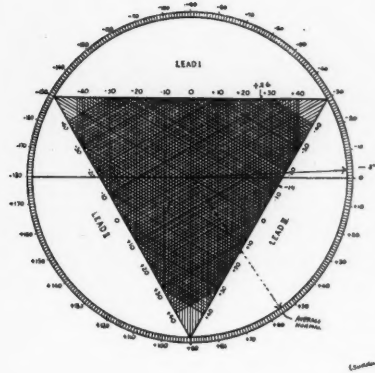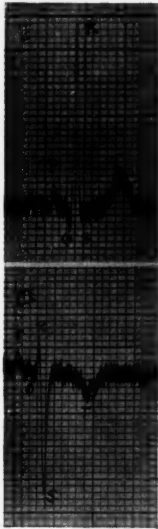
FIG. 3.   Lead I = +28 − 2 = +26
          „ III = −18 + 4 = −14

1½ Hours	1 Week	2 Weeks	3 Weeks	5 Weeks	4 Months
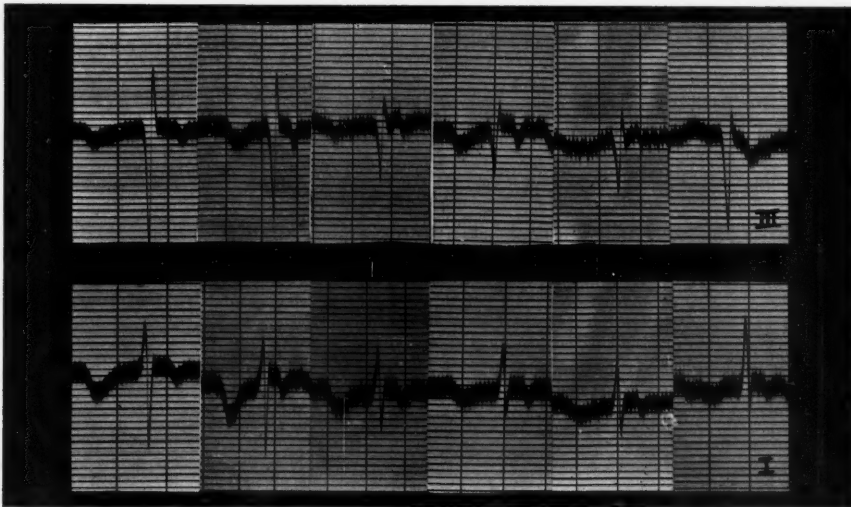
Axis	+123°	+113°	+104°	+90°	+69°	+64°

FIG. 12.

THE STORAGE OF IRON FOLLOWING ITS ORAL AND SUBCUTANEOUS ADMINISTRATION [1]

By CYRIL J. POLSON

(From the Department of Pathology of the University of Leeds)

THE results of oral administration of iron form some of the earliest medical observations of the past century. It is not proposed to re-open the classical controversy concerning the absorption of iron from the intestine, for it is abundantly proved that this occurs no matter which preparation of iron is used. It was in this controversy that Bunge and Quincke (1895–6) played a prominent part. In 1896 and 1897 Lapicque and Guillemin gave haemoglobin to animals but obtained irregular results; these appeared to be due to differences in the sex of the animals and also due to their state of health. Cloetta, in 1900, demonstrated the absorption of iron from the duodenum. Hofmann in the same year showed that the administration of medicinal preparations of iron led to its accumulation in the spleen, liver, lymphatic glands, and the bone marrow. In present results the principal site of storage was the liver, and no excess of iron was found in the bone marrow. Müller, in 1901, demonstrated accumulation of iron in the liver following oral, subcutaneous, and intravenous administration of iron. Schaffidi (1909) raised the liver iron content from 0·009 per cent. to 1·10 per cent. by feeding animals with 'paranukleinsaurem eisen'. Gróh, in 1913, failed to find any iron excess in the organs after pigs were fed on 'blutmehl', rich in haemoglobin. On the other hand, Williamson and Ets, in 1927, showed that a diet rich in iron, one containing a quantity of ox spleen, caused an increase in the splenic iron content of dogs from 27 mg. to 60 mg., while the liver iron content was raised from 119 mg. to 303 mg.

Gottleib, in 1880, administered iron subcutaneously in order to study its excretion, and found that 70 per cent. of the iron was excreted in the faeces. Ziegler, in 1894, stated that he had found an accumulation of iron in the spleen, bone marrow, lymphatic glands, and the liver when iron was administered by this route. He also mentioned that iron in the liver was restricted to the Kupffer cells and none was found in the liver cells. In view of the present results it seems likely that his experiments were not prolonged for more than two or three months. The full text of his observations cannot be traced. Schurig, in 1898, gave haemoglobin subcutaneously, and found that there

followed an accumulation of iron in the liver, spleen, bone marrow, and kidney. Müller (1901) produced an accumulation of iron in the liver by giving it sub-cutaneously.

In the present paper the results were obtained by a combination of chemical and histological examinations, a method used only by Ziegler, and, as stated, his experiments were of short duration, whereas in the present series the oral experiments lasted for as long as sixteen months and the subcutaneous one for as long as eleven months. The original object in view was to control the observations obtained when iron was given intravenously (Polson 1928 and 1929). Although the rate of iron storage was slower the process was probably identical no matter what the mode of administration.

Dosage and Technique.

(a) *Oral administration of iron.* Four rabbits were used. During the first few months of experiment they received daily doses of 10 c.c. of undiluted dialysed iron (B.D.H. Ltd.), containing 0·5 grm. of iron, mixed with their food. Owing to expense this was later changed to Liquor Ferri Perchloridi (B.P.) in daily doses of 10 c.c. of a 25 per cent. dilution of the strong preparation; each dose contained 0·5 gm. of iron. The experiments lasted from 172 to 450 days, and daily observations were made to determine the amount of food and thus the approximate amount of iron eaten. From 55 grm. to 100 grm. were administered, and approximately from 50 grm. to 70 grm. of iron were eaten. The rabbits were killed and their organs were examined by the technique described elsewhere (1928).

(b) *Subcutaneous administration of iron.* Eight rabbits were used. Five received a single dose of undiluted dialysed iron (B.D.H. Ltd.) of from 10 to 20 c.c., one half of the total dose being injected into each flank. Three rabbits, those of experiments 7, 11, and 12, received more than one dose, the total dosage being 40·5 c.c., 20 c.c., and 11·4 c.c. respectively. After intervals, which ranged from one to eleven months, the rabbits were killed and their organs examined.

Chemical Findings.

(c) *Oral administration experiments.* In Table I the 'normal' iron content of rabbit organs is given and the protocols of these experiments are set out in Table II. The maximum storage of iron in the liver of any of these rabbits was 85·81 mg., observed in the liver of experiment 2 at the end of 228 days. Considerable variation was noted, since the liver of experiment 3, that of a rabbit fed with iron for 263 days, contained but 25·62 mg. There was no excess of iron in the lungs, and the slightly high figure obtained in the lungs of experiment 4, namely 7·3 mg., was accounted for by the presence of haemor-rhages and experimental error. The kidneys of experiments 1 to 3 contained an excess of iron whereas, on the chemical evidence, the spleens of all these

rabbits held less than the healthy content of iron, but this was not supported by the histological evidence.

(b) *Subcutaneous administration experiments.* The protocols of these experiments are set out in Table III. The anticipated high iron content of the liver was obtained by this method of administration. The liver held 10·98 mg. at the end of one month, and the maximum figure recorded was at eight months in experiment 10 when 408·85 mg. were found in the liver, following the administration of one gram of iron. The livers of rabbits killed at intervals which increased in length showed that there was a steady increase in the quantity of iron held by the liver, but certain variations were noted. Thus in experiment 11, although 1 grm. of iron was given, the liver iron content at the end of ten months was but 91·06 mg. None of the lungs contained an excess of iron. With the exception of experiment 5, all the kidneys from the remainder of the experiments held an excess of iron which ranged from 2·16 to 6·67 mg. The splenic results varied, but there was an excess of iron present except in those of experiments 10 and 11. The highest result obtained was an excess of 7·73 mg. Even at the end of eleven months, after the administration of the smallest dose in the series, there was a quantity of iron still *in situ*. This was collected and examined in experiment 11; the dried subcutaneous tissue held 3·70 per cent. of iron, and at an approximate estimate, 309 mg., or one-third of the dose, was still beneath the skin.

Histological Observations.

(a) *Oral administration experiments.* The principal feature was an accumulation of iron in the liver. The outer thirds of the hepatic lobules contained a quantity of diffuse iron, while there was a fair amount of it elsewhere. At the periphery of the lobules coarse granules of iron were seen in the liver cells, gathered around their nuclei, while in other parts of the lobules fewer and smaller granules were also seen. A few Kupffer cells contained iron, but there were no iron giant cells save a small clump in the liver of experiment 3. These held little iron and were probably present at the outset of the experiment. On rare occasions such giant cells were seen in the livers of 'normal' animals.

There was a small accumulation of iron in the spleen, although this was not detected by the chemical examination. Thus a number of small iron aggregations and cells containing iron were seen scattered through the splenic pulp. The quantity of iron present was at no time as large as that seen in the spleen after the administration of iron intravenously. The caecum and kidney contained an excess of iron demonstrable both in diffuse and granular form. The bone marrows were healthy but contained no excess of iron, neither were they unduly active. The lungs were free from iron.

(b) *Subcutaneous administration experiments.* The livers illustrated similar stages of iron storage observed after the intravenous administration of iron, and although the time intervals were somewhat longer, the appearances of the

livers in these two groups of experiments were similar. At the end of from one to two months the only demonstrable iron in the liver was that held by the Kupffer cells. Granules of iron in the liver cells at the periphery of the lobules appeared later, and by the end of eight months the livers had an appearance similar to that observed in the longer experiments after the administration of iron by the intravenous route ; there was, however, more iron present, and granules of iron were more widespread in the liver lobules. An exceptional result was noted in experiment 7 at the end of five months. So widespread was the distribution of iron that all the liver cells appeared to be choked with iron granules. At seven months, as seen in experiment 8, there was a quantity of diffuse iron throughout the lobules, and the cells of the outer thirds were packed with coarse granules of iron ; the Kupffer cells held iron, and there were a number of iron giant cells at the periphery of the lobules. Many of the portal tracts showed an increase in the fibrous tissue present ; they were unduly cellular and prolonged in length, the appearance suggesting an early cirrhosis. At eight months, in experiments 9 and 10, there was a greater degree of iron storage, and granules of iron were seen also in the cells in the central zones of the lobules. There was an early cirrhosis of the liver in experiment 9. At ten to eleven months, in experiments 11 and 12, there was much less iron present in the livers, but its distribution was similar to that seen in the others.

With the exception of experiment 5, there was accumulation of iron in the spleens of all the rabbits, and iron aggregations of moderate size, somewhat larger than those seen after oral administration of iron, were found in the splenic pulp. In experiment 5 there was a faint diffuse deposition of iron in the cells of the first convoluted renal tubules, while in the remainder of the experiments a quantity of granular iron was found in this situation. The bone marrows held no excess of iron, neither did they show undue activity. In the pancreas of experiment 5 there was a parasitic lesion, and at its periphery there were cells which gave a diffuse berlin blue reaction. No iron was demonstrated in the pancreatic glands of the other rabbits. There was iron in the medulla of the suprarenal glands present in diffuse form in those of experiments 9, 10, and 12, while in that of experiment 9 granular iron was also demonstrated. No iron was found in the suprarenal cortex. The coeliac glands contained a quantity of iron, but little was found in the mesenteric group. Granules of iron were present in the epithelial cells of the salivary gland of experiment 9. Demonstrable iron was absent from the lungs of all experiments.

Discussion.

It was shown that the principal site of iron storage following its oral administration was the liver. This confirmed the results of the intravenous experiments. At the same time, although much larger doses of iron were given by mouth, only a relatively small amount accumulated in the liver. The

variation in the quantity so stored was almost certainly dependent upon the appetite of the rabbit.   Not only was the liver the principal site of storage but also the distribution of the iron corresponded to that seen after intravenous administration of iron.   The scarcity of iron giant cells in the oral experiments may be accounted for by the fact that iron reached the liver more slowly and in smaller amounts.   It appears that the formation of these giant cells occurred only when there were large amounts of iron to be dealt with, especially when there was urgent need for action following the intravenous administration of iron.

The caecum and kidney contained an excess of iron, suggesting that these organs probably played a part in its excretion, for the iron excess was greater when the liver iron was at a higher level.   Whipple (1922) observed that the administration of haemoglobin did not alter the iron content of the bone marrow, and the present results are in agreement.   Neither was there evidence to show, as suggested by von Noorden, that iron stimulated the bone marrow, for in no case was there unusual activity.   Iron was absent from the lungs as was anticipated, for that seen after intravenous administration remained in the lungs solely as a result of the accident of pulmonary embolism.

When iron was administered subcutaneously the liver was the principal site of storage, and there was a steady accumulation of iron as the experiments increased in duration.   Although the stages of iron accumulation in the liver were at longer intervals, they were precisely those observed after intravenous administration.   The histological features were in close agreement, and the only process not observed was the formation of iron giant cells.   Since there were a number of these present it may be permissible to assume that they were produced by fusion of Kupffer cells as before.   The only difference of note between the results of subcutaneous and intravenous methods of administration of iron was that by the former route a much greater degree of iron storage was produced in the liver.

Certain variations require comment.   In experiment 7, at the end of five months every liver cell was choked with iron, an appearance which suggested that there was a much greater quantity of iron present than was determined, namely, 133·1 mg.   This was an exceptionally small liver, for it weighed but 25 grm. as compared with the average range of weight of from 50 grm. to 90 grm.   The small size of this liver probably caused all the cells to take iron, whereas in a liver of average size only those cells at the periphery of the lobules were charged with iron, the quantity of iron present being the same in each liver.

The low iron content of the liver in experiment 12, being but 70·24 mg. at the end of eleven months, was probably accounted for by the small dose administered.   The low iron content of the liver in experiment 11 may possibly be due to the fact that the iron was given in divided doses of 2·5 c.c. per week, but no definite opinion is offered.

The iron excess in the spleen was greater than that found after oral, but

definitely lower than was found after intravenous administration.   This supported the view that the high iron content of the spleen in the latter experiments was the result of a transfer of iron from the lungs to the spleen.

The appearance of iron in the medulla of the suprarenal gland and in the epithelium of the salivary gland is not understood, but it is suggested that these are areas of overflow of iron from the liver.

There was excess of iron in the caecum and the kidneys.   In the latter the iron was more than in any of the previous experiments and was thus related to the higher level of iron in the liver.   The evidence suggested that the kidneys excreted iron when the liver iron content rose above a level of about 20 mg.

Iron in the coeliac lymphatic glands was probably derived from the liver and was seen only when there was a high iron content in that organ.

In two livers there was an early cirrhosis, but it is not permissible to claim these as of experimental production, since in a series of twenty-six 'healthy' rabbits three had cirrhosis of the liver (Polson, 1929).   However, an attempt to produce cirrhosis of the liver by massive dosage with iron is now in progress.

In conclusion, the rate of storage following the administration of iron by the three routes may be compared.   When from 256 to 448 mg. were given by the intravenous route there were between 120 and 184 mg. excess of iron in the liver after intervals of from three to twelve months; following subcutaneous administration of 1 gm. of iron there were 398 mg. excess at the end of eight months, while the oral administration of 90 grm. resulted in the storage of only an excess of 81·8 mg. at the end of eight months.   Thus when due allowance is made for the quantity of iron given the intravenous is the most speedy and the oral route the slowest.   For experimental purposes the subcutaneous route was the best, since a larger amount of iron was stored in the liver and the danger of intravenous administration, namely, pulmonary embolism, was avoided.

Summary.

1. In these experiments the liver is the principal site of iron storage. A smaller amount was stored in the spleen and lymphatic glands.

2. The rate of storage of iron in the liver was faster after subcutaneous than after oral administration, but neither was as fast as the intravenous route.

3. The process of iron storage in the liver was probably identical irrespective of the mode of administration.

4. The small excess of iron in the spleen supported the view that the greater amount found there after intravenous administration was the result of a transfer of iron from the lungs to the spleen

5. The caecum and kidneys contained an excess of iron and were probably concerned in its excretion.

6. Excess of iron in the bone marrow was not observed neither was there undue activity of its cells.

7. The lungs played no part in the metabolism of iron.

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TABLE I. *The Iron Content of Healthy Rabbit Organs.*

Organ.	Percentage of Iron Dry Weight.	Total Iron in mg.
Liver	0·056	6·30 (3·25 to 10·06)
Kidney	0·075	1·38 (0·87 to 2·15)
Spleen	1·289	2·13 (0·78 to 4·01)
Lung	0·117	1·44 (0·44 to 4·23)

TABLE II. *Protocols of Rabbits given Iron by Mouth.*

Experiment.	Rabbit.	Duration of Experiment in Days.	Iron Dosage in grm.		Liver Iron Content.			Kidney Iron. Gross Content in mg.	Spleen Iron. Gross Content in mg.	Lung Iron. Gross Content in mg.
			Given.	Eaten.	% Dry Weight.	Gross Content in mg.	Net Excess in mg.			
1	65	172	70	60	0·481	42·95	35·07	1·89	0·58	1·31
2	64	228	90	65	1·337	85·81	81·78	1·73	0·81	1·09
3	87	263	100	70	0·300	25·62	21·08	5·75	0·77	1·40
4	88	450	55	50	0·766	62·72	54·40	1·17	1·37	7·30

TABLE III. *Protocols of Rabbits given Iron by the Subcutaneous Route.*

Experiment.	Rabbit.	Duration of Experiment in Months.	Dosage of Iron in c.c.	Liver Iron Content.			Kidney Iron. Gross Content in mg.	Spleen Iron. Gross Content in mg.	Lung Iron. Gross Content in mg.
				% Dry Weight.	Gross Content in mg.	Net Excess in mg.			
5	159	1	20	0·110	10·98	3·73	1·23	5·96	0·73
6	160	2	15	0·384	40·68	34·38	6·31	4·02	2·61
7	76	5	40·5 c.c. in divided doses	4·905	133·14	129·61	5·03	Not examined	Not examined
8	157	7	20	1·432	242·93	233·92	6·42	11·05*	0·88
9	161	8	20	1·488	277·03	267·26	4·90	„	1·76
10	155	8	20	2·246	408·85	398·20	5·64	2·41	0·91
11	82	10	20 in divided doses	0·718	91·06	85·37	7·94	1·82	4·35
12	121	11	11·4 in 2 doses	0·418	70·25	62·12	3·94	3·87	0·97

* Net Iron Excess of this spleen was 7·73 mg.

OBSERVATIONS ON THE RESPIRATORY EXCHANGE AND BASAL METABOLIC RATE IN PULMONARY TUBERCULOSIS [1]

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In a disease producing marked and extensive changes in pulmonary tissue we should expect to find alterations in respiratory function. Metabolic changes govern the respiratory exchange, but structural changes in the lungs may affect their function as a bellows. It is important to keep this distinction in mind. It is the aim of this paper to show what these changes are and to consider them in the light of their effect on treatment and prognosis. The cases have been studied from two points of view: (1) the information which can be derived from a single reliable estimation of the external respiratory exchange and the basal metabolism, and (2) the information derived from a series of periodical examinations on the same case.

The factors which will be discussed are the pulse, respiration rate, volume per respiration, pulmonary ventilation, the percentage of carbon dioxide in the expired air, the respiratory quotient, and the basal metabolic rate.

In all save the most acute forms of pulmonary tuberculosis, two pathological processes may be recognized, one destructive passing into caseation and softening; the other defensive leading to proliferation of connective tissue and fibrosis. The clinical investigation of a case of pulmonary tuberculosis should determine not merely the extent of the disease but also the stage to which the destructive process has advanced and the degree of repair effected by the defensive mechanism.

Aided by skilled radiological investigation it is possible to form an opinion as to whether the disease is in the stage of infiltration, or whether softening of the caseous material and excavation has commenced (or whether actual cavities are present), and at the same time to estimate the degree of defensive fibrosis.

A tuberculous lesion may exist in the lungs without producing any symptoms of ill health. This is the condition which the clinician indicates when he says that the disease is arrested.

Again, a lesion ordinarily latent may in certain adverse circumstances produce symptoms which in time may become aggravated and associated with extension or changes in the lesion. Some symptoms are obviously due to the

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focal lesions in the lung, e.g. cough and the expectoration of sputum, others are presumably due to the escape of toxins into the circulating blood; such are pyrexia, tachycardia, wasting, night sweats, malaise, headache, vague pains, dyspepsia, and the like. Generally speaking, toxaemic symptoms are found where caseation and softening are taking place but are absent where reparative changes predominate. We may classify our cases according to the type of lesion we believe to be present in the lung—infiltration, softening, or fibrosis,— or according to whether the symptoms are mainly toxaemic or focal in character. Both toxaemic and focal symptoms may, of course, be found in the same case. Both these classifications will be used in discussing the cases described in this paper.

Methods Employed.

The method employed was the Douglas Bag method which it is unnecessary to describe in detail, particulars of the technique used having been given in a previous paper (1). The experiments were all made under basal conditions and on carefully chosen male patients who by trial tests had been accustomed to the procedure. The majority of the patients examined had been in hospital for more than a week before the first examination was made. In this way falsely high results due to unaccustomed surroundings and excitement were avoided and an approximately stable degree of rest secured. The surface area was determined from the height-weight chart of Boothby and Sandiford and the calories per litre of oxygen absorbed from the table of Luntz and Schumberg.

Grouping of the Cases.

The results of the determination of the respiratory exchange and basal metabolism have been divided into two classes according to whether the basal metabolism is increased or normal. These classes have been subdivided into two groups according to the duration of the disease, for if it is known that the disease has existed for a year or more the case may be looked upon, from a clinical standpoint, as being of the chronic type. There are thus four groups of cases to be considered.

Group I.
　Basal metabolism raised; duration less than one year.

Group II.
　Basal metabolism raised; duration more than one year.

Group III.
　Basal metabolism normal; duration less than one year.

Group IV.
　Basal metabolism normal; duration more than one year.

TABLE I.

| | Pulse. | Respirations. | Litres of Expired air per min. | Volume per Respiration c.c. | Analysis of Expired air % | | O_2 consumed per min. c.c. | CO_2 eliminated per min. c.c. | Respiratory Quotient. | Basal Metabolic Rate. |
					CO_2	O_2				
Normal	59	13·5	4·974	460	3·68	16·57	224	182	0·81	
Group I	83	15	7·560	486	3·09	17·24	291	231	0·79	+23 %
Group II	83	16·5	7·535	463	2·74	17·51	271	204	0·75	+18 %
Group III	76	13	6·091	498	3·32	17·06	244	200	0·82	−0·5 %
Group IV	70	14·5	6·358	466	2·94	17·48	228	185	0·81	−1·0 %

Table I gives the average figures for the various factors concerned in the respiratory exchange and basal metabolic rate of thirty-eight cases of pulmonary tuberculosis soon afte   admission to hospital.   The figures are the means of the first, or first t..   ..inations when two examinations were made within a few days of each other.   The normal standard which is included is the average of a series of determinations on twenty-four cases made by Carpenter (2) using methods of indirect calorimetry.

Basal Metabolism.

No increase in the basal metabolism in pulmonary tuberculosis was found by Barbour (3), McBrayer (4), Kocher (5), and Brock (6), and McCann and Barr (7) found that in the majority of cases it was normal or only slightly above normal.   On the other hand Grafe (8, 9), Dautrebande (10), Cordier (11), Vogel-Eysern (12), Lanz (13), Suan (14), Bosco (15), Brieger (16), and Ahlenstiel (17), have all reported cases in which the basal metabolic rate was definitely increased.   The following are the chief points arising from their work—there may be an increased basal metabolic rate apart from rise of temperature (Grafe, Dautrebande, Brieger), the basal metabolic rate may vary with the type of case (Lanz), it varies according to the severity of the disease (Vogel-Eysern, Lanz, Suan, Brieger, Ahlenstiel), it is an aid in judging the progress of a case (Cordier, Vogel-Eysern, Lanz, Suan, Bosco, Brieger), and it may be of help in judging the efficacy of treatment (Vogel-Eysern).

The majority of continental workers have recorded a definite increase in basal metabolism, while American investigators have found it to be within normal limits or only slightly raised.   It is possible that these differences are due to the diversity of the lesions and clinical features, and to the duration of the rest to which the patient has been subjected before the examinations.

The basal metabolism in a large group of healthy men will fall within plus or minus 10 per cent. of the average.   This is taken as the normal standard in discussing the following results.

The basal metabolism of 38 cases of pulmonary tuberculosis has been investigated.   In 19 it was higher than plus 10 per cent. (the average being plus 20·5 per cent.), and in the other half it was within plus or minus 10 per cent. of the normal (the average being minus 0·75 per cent.).

Considering these groups from a clinical point of view it was evident that they corresponded closely with the severity and type of the disease. All except four of the cases with increased basal metabolic rates had pyrexia and marked general symptoms as opposed to symptoms of focal origin. The exceptions were first a case, who, though afebrile while in hospital, had been running a temperature for four weeks before admission and was clinically a toxic case. Secondly, an early case, afebrile while in hospital, who had had a recent haemoptysis and night sweats; his symptoms were toxic rather than focal in origin, and softening of the local lesions was shown by X-rays. Another case was afebrile while in hospital but had had pyrexia for several weeks before admission. He was an early, active case with toxic symptoms. The last was afebrile and had no general symptoms. Three out of these four cases, then, were active, with general symptoms.

In the group of cases with a normal basal metabolic rate there was only one case with pyrexia, the other cases were non-toxaemic in character, the predominant symptoms being focal in origin. This exception is discussed later.

From the above considerations it is justifiable to conclude that in pulmonary tuberculosis an increased basal metabolic rate is associated with signs of tuberculo-toxaemia.

Although the basal metabolic rate may change rather quickly, as will be shown later, it is worth while to consider briefly the anatomical lesions present in these cases.

TABLE II.

	Softening	Infiltration only	Fibrosis
Basal metabolic rate increased	12	5	2
Basal metabolic rate normal	0	3	16

In Table II they are classified according to whether they show signs of infiltration only, softening, or fibrosis. The result is striking. No destructive changes were present where the basal metabolic rate was normal, whereas these changes were evident in 63 per cent. of the cases in which the basal metabolic rate was increased and were in all cases associated with pyrexia and general symptoms.

Infiltration only was associated with five cases in which the basal metabolic rate was raised and three in which it was normal.

Fibrosis was present in approximately 84 per cent. of the cases with a normal basal metabolic rate and in 11 per cent. of the cases with an increased rate.

Pulmonary Ventilation.

The average normal pulmonary ventilation under basal conditions is about 5 litres per minute; it may vary between 4 litres and 6 litres. From Table I it will be seen that in pulmonary tuberculosis the cases with a normal basal metabolism have a pulmonary ventilation of approximately 6 litres per minute,

that is a little above normal, and that those with an increased basal metabolic rate have a pulmonary ventilation averaging 7·5 litres per minute, which is considerably above the normal value. In many cases the increase in the pulmonary ventilation is out of proportion to the increase in metabolism. In Groups III and IV the basal metabolic rates are within normal limits, but the corresponding figures for the pulmonary ventilation are increased in a number of cases.

McCann (18) found that in five cases of pulmonary tuberculosis the pulmonary ventilation was twice that of normal subjects. Assuming that the dead space was 130 c.c. he calculated the effective pulmonary ventilation, that is, the amount of air entering the alveoli in which actual exchange of gases with the blood takes place, and came to the conclusion that it was greater in pulmonary tuberculosis than in normal individuals.

I am not yet in a position to discuss this question fully, but Dautrebande (19) has found an increase in the dead space in cases of pulmonary tuberculosis with advanced lesions. It is most probable that in some of these cases an increase in the physiological dead space accounts for the pulmonary ventilation being higher than would be expected for the corresponding basal metabolic rates. The physiological dead space was determined in three cases with normal basal metabolic rates.

TABLE III.

	Basal metabolic rate	Pulmonary ventilation	Dead space	Effective pulmonary ventilation
Case 39	−1·5	5·086 L	178 c.cs.	2·327 L
Case 40	−1·5	7·532 L	255 c.cs.	2·942 L
Case 34	−8·0	6·910 L	195 c.cs.	2·815 L

Case 39 was diagnosed as ' debility '; his dead space was normal. Case 40 had a pleural effusion without a pulmonary lesion, and Case 34 had an effusion with a definite lung lesion ; both these cases had an increased dead space. The effective pulmonary ventilation in the three cases was approximately the same, roughly 2·5 litres per minute, the actual pulmonary ventilation was approximately 5 litres per minute in the patient with debility, 7·5 litres and 7 litres per minute respectively in the two patients with pleural effusion. In other words, to obtain the same effective pulmonary ventilation as a normal person the two patients with pleural effusions had to increase their pulmonary ventilation by 1 to 1½ litres per minute more than the normal. This must be an important factor in the production of dyspnoea in cases of pleural effusion. In neither case was the amount of fluid large.

Increased pulmonary ventilation in pulmonary tuberculosis, therefore, may be caused by toxaemia or focal lesions.

The Pulmonary Gases.

The percentage of carbon dioxide in the expired air varied considerably. Dautrebande (19) has shown that the more extensive the pulmonary lesion the

greater is the deviation from normal, and the greater the pulmonary ventilation the lower is the percentage of carbon dioxide and the higher the percentage of oxygen in the expired air. The relation between the extent and duration of the disease and the percentage of carbon dioxide in the expired air is shown in Table IV.

TABLE IV.

	% of CO_2 in expired air	Extent of disease. Zones affected	Duration
Group III	3·32	8·75	Less than one year
Group I	3·09	4·5	,, ,, ,, ,,
Group IV	2·94	4·4	More than one year
Group II	2·74	5·0	,, ,, ,, ,,

The extent of the disease has been estimated from the X-ray appearances, the radiogram being divided into zones according to the following classification in use at the Brompton Hospital.

Zone 1. From the apex to the lower margin of the second costal cartilage.

Zone 2. From the lower margin of the second costal cartilage to the lower margin of the fourth.

Zone 3. Below the fourth costal cartilage.

The figures are in agreement with Dautrebande's.

There is least deviation from the normal in the group of cases where the disease is least extensive, the basal metabolism normal and the duration less than twelve months; the deviation from normal is greatest when the disease is most extensive and the duration more than twelve months.

Table I shows that the respiratory quotient is a little less than normal in the cases where the basal metabolism is increased. This lowering of the respiratory quotient is more marked in the cases of longer duration. It is probably due to an alteration in the acid base equilibrium rather than to metabolic changes.

Dautrebande (20) has shown that in the terminal stages of pulmonary tuberculosis the respiratory quotient may fall to below 0·70. He suggests that where bronchi are blocked with mucus there are regions of stagnant air which increased ventilation does not renew, so that the blood is less and less oxygenated and carbon dioxide increases; this combines with bicarbonate to maintain the pH, the quantity of carbon dioxide in the expired air diminishes and the respiratory quotient falls. Such alterations would account for the abnormally low respiratory quotients found in Cases 11 and 16. In the latter case they were associated with alterations in the physical signs.

The Pulse-Rate.

In pulmonary tuberculosis the pulse-rate is unstable, even a slight amount of exertion causing a considerable increase in rate. In the cases recorded, the pulse-rate was taken with the patient under basal conditions, which accounts for the comparatively low rates, but it is worth drawing attention to the facts

that the basal metabolism and pulmonary ventilation were increased in three cases where the pulse-rate varied from 56 to 68, and in the group of cases with a normal basal metabolism there were six in which the pulse-rate was between 57 and 68, although it is usually found that an infrequent pulse is uncommon in pulmonary tuberculosis. It would appear not to be so uncommon when taken under basal conditions. In Class I (Group 1 and 2) the average pulse-rate is 83, and the average basal metabolic rate is plus 20·5 per cent.; in Class II (Groups 3 and 4) the average pulse-rate is 73 and the average basal metabolic rate is 0·75 per cent. There is a general tendency for the pulse-rate to increase with increased metabolism. Again, speaking generally, the pulse-rate varies directly with the basal metabolic rate when a series of determinations are considered, but there are exceptions to this. The same relations and exceptions are found in exophthalmic goitre, but there the pulse-rates and basal metabolic rates are higher.

Respiration.

There was a slight difference in the average respiration rate in the two classes of patients examined, it being slightly higher in those with increased basal metabolism. There was a tendency for the respiration rate to fall as the basal metabolism and pulmonary ventilation became lower, but the variations were so small as to be of no practical importance.

The average volume per respiration in pulmonary tuberculosis was found to be slightly greater than normal. The individual variation was considerable, but the volume was fairly constant for a given individual.

In a number of cases estimations of the respiratory exchange were made from time to time during a patient's stay in hospital and the basal metabolism calculated. The most striking factor common to all is that the pulmonary ventilation rate varies directly with the basal metabolic rate, although the intervals between these curves vary in different cases. The pulse-rate tended to follow the basal metabolic rate, but not so closely as did the pulmonary ventilation rate.

The following is a selection of typical cases illustrating the changes observed when repeated examinations of the respiratory exchange are made.

Case 6. Fig. 1 had a recent extensive lesion showing signs of softening. His evening temperature was raised at first but became normal under treatment. His general condition improved with rest in bed and a course of sanocrysin.
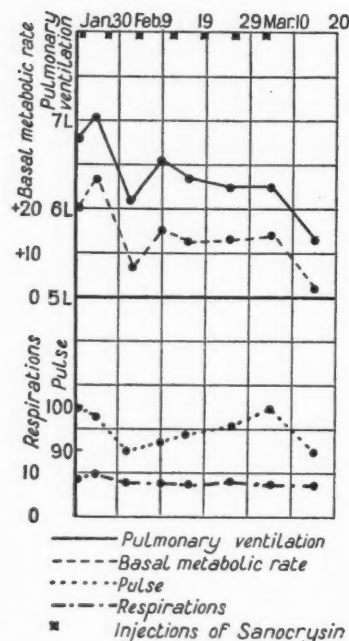
Fig. 1.
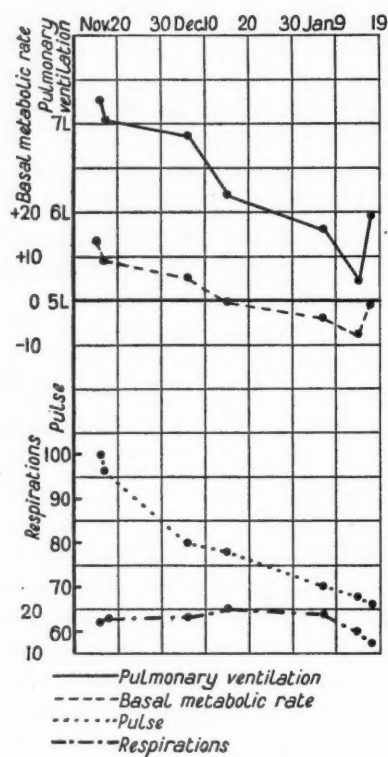
Fig. 2.

Case 12. Fig. 2 was similar to Case 6. He had a recent lesion showing softening and a slight evening temperature which soon became normal. He made very definite progress while under treatment. The first estimation of the respiratory exchange was made only after he had been in hospital and in bed for twelve days. He was put on absolute rest after this, and his basal metabolic rate and pulmonary ventilation fell steadily. The last estimation, made after the patient was getting up all day, was increased. The percentage of carbon dioxide in the expired air was slightly less than normal.

Case 16. Fig. 3 was one of chronic pulmonary tuberculosis with marked fibrosis and recent exudative changes in the left lung. There was a slight increase in the percentage of carbon dioxide in the expired air as he improved. The respiratory quotients of the first three examinations were abnormally low. The patient was very ill, complaining of vague symptoms, which culminated
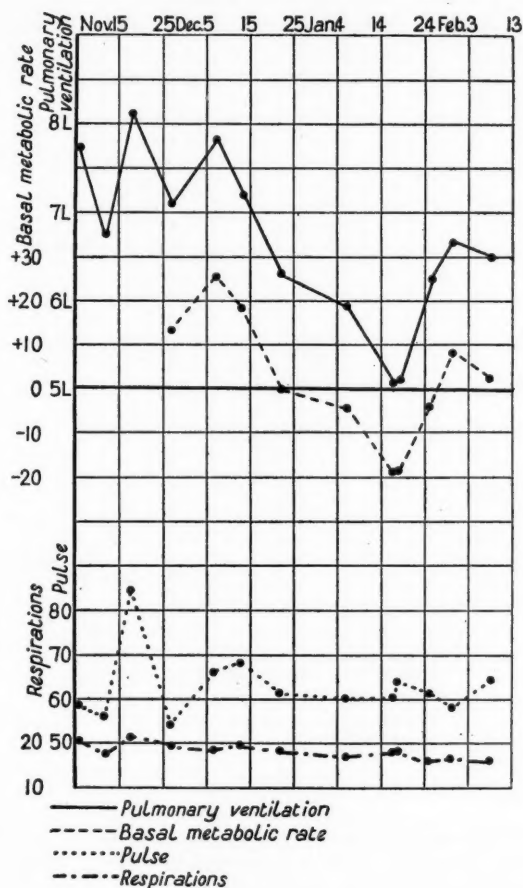
Fig. 3.

with an attack of vomiting and rise of temperature on 18.11.26, when the excessively low respiratory quotient of 0·56 was obtained. At this time there were definite signs of extension of the disease, with increased sputum. The patient's temperature became normal and he began to show signs of improvement about a week after this.

Case 21. Fig. 4 gave a recent history of pulmonary tuberculosis; there was considerable infiltration of the lung tissue but a marked tendency towards fibrosis. For the first six weeks his temperature was irregular; it then became normal. He had been resting in bed for three weeks before the first estimation

of his respiratory metabolism was made, and presumably it was higher on admission. His general condition was good and there was no marked loss of weight. The percentage of carbon dioxide in the expired air was always more than three, never abnormally low as in the following cases.
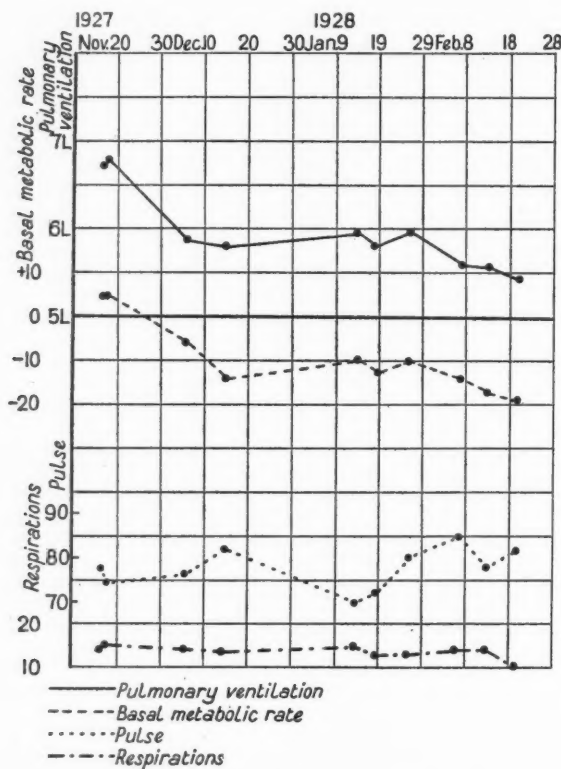
FIG. 4.

Case 11. Fig. 5 was a patient with a rapidly progressing lesion, accompanied by fever and marked loss of weight; there was everything to suggest a bad prognosis. On admission X-ray examination showed much infiltration but no softening; the basal metabolic rate was increased, but not markedly so; the pulmonary ventilation was considerably increased. The relatively low basal metabolic rate may have been partly due to undernutrition and wasting. On absolute rest and a course of sanocrysin the pulmonary ventilation and basal metabolic rate fell for a time, then began to increase again. At this time a second X-ray examination was made which showed that softening was taking place and the infiltration increasing. On a second course of sanocrysin, and while still on absolute rest, there was again a slight tendency for the metabolic rate to fall, but on the whole the basal metabolic rate and the pulmonary ventilation showed no marked fall during the treatment. The percentage of carbon dioxide in the expired air and the low figures (on two occasions) for the respiratory quotients are other points of interest. The patient went home at his own request and died shortly afterwards.
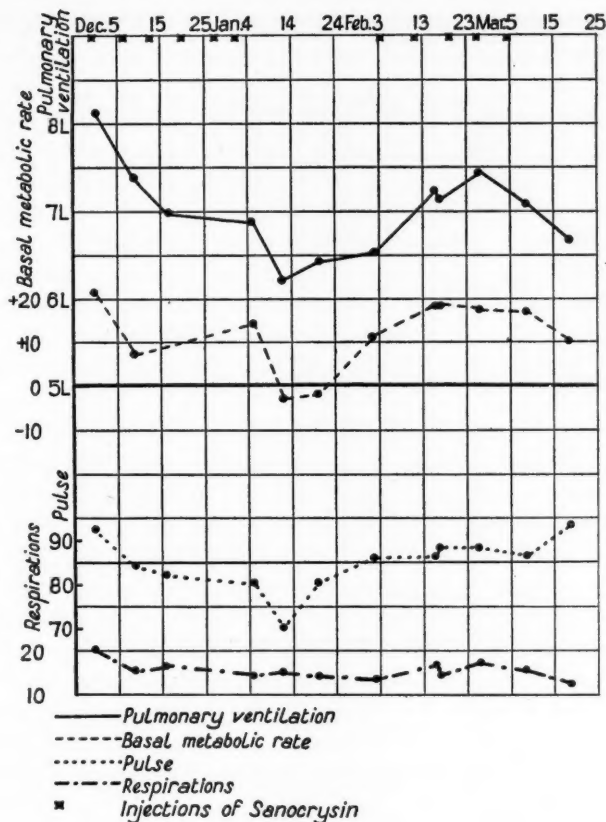
Fig. 5.

Case 13. Fig. 6 was one of chronic pulmonary tuberculosis showing marked softening and fibrosis. There was marked fever on admission to the hospital; this gradually improved, as did his general condition. He had lost considerable weight. Clinically, the prognosis was bad. The percentage of carbon dioxide in the expired air was low but increased slightly during the period in hospital.

The cases cited above are typical and the following conclusion may be drawn:

1. In a quiescent case or a case in which fibrotic changes preponderate, the basal metabolism is normal and practically the same from time to time. The pulmonary ventilation may be increased.

2. Where improvement is taking place, there is a gradual fall in the basal metabolic rate, with a corresponding fall in the pulmonary ventilation.

3. If improvement is not taking place, the basal metabolic rate and pulmonary ventilation are increased and remain at a higher level than normal.

An exception to this may be found if there is marked loss of weight, when the basal metabolic rate may not be much increased, but the pulmonary ventilation will be increased.
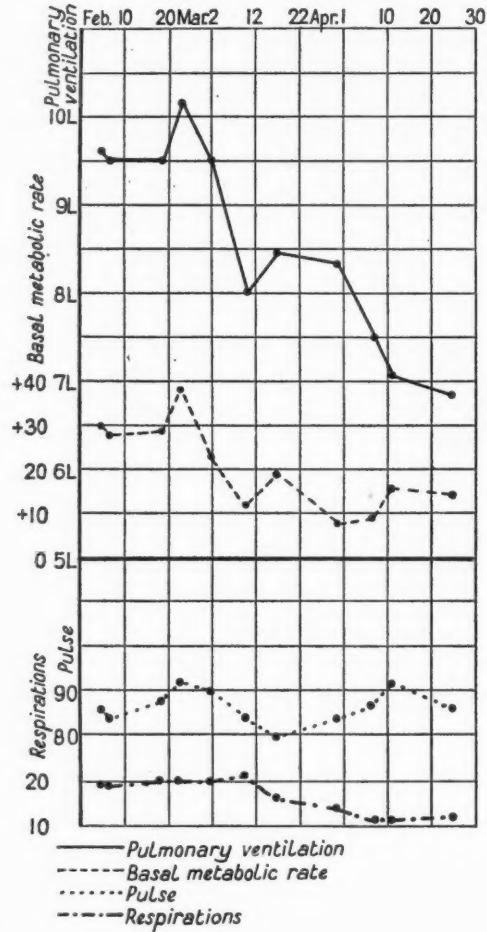
FIG. 6.

Discussion.

The basal metabolism in certain cases of pulmonary tuberculosis is raised (see Table I), but in favourable cases it becomes lower if the patient remains in bed or is on absolute rest. A similar change is found in other diseases. Du Bois (21) found that, in cases of exophthalmic goitre, rest in bed for a week or more caused a drop in metabolism of more than 10 per cent., this fall not being due to falsely high readings on the first test when the patients were un-

accustomed to their surroundings and the procedure of examination. This has been recently confirmed by Möller (22), who has found a fall in the basal metabolic rate of from 10 to 20 per cent. in cases of Graves' disease treated by rest and good food.

Increased metabolism necessitates an increase in the pulmonary ventilation with increased movement of the lung tissue. It is one of the tenets of the treatment of tuberculosis to put the affected organ at rest and to keep it at rest until healing has taken place. With an organ like the lung complete rest cannot be obtained, but methods such as artificial pneumothorax and more drastic surgical measures, such as thoracoplasty, have the same object in view, that is to rest the diseased lung as much as possible. In sanatorium treatment also, rest is the most fundamental therapeutic measure. It has also been demonstrated experimentally that rest contributes greatly to the healing of pulmonary lesions.

The data discussed in this paper give not only a scientific justification for the importance attached to rest in the treatment of pulmonary tuberculosis, but also a method by which its effectiveness can be measured. Measurements of the pulmonary ventilation give a better idea of the functioning of the lung than any other single factor.

When the basal metabolism is above normal, as is usually the case when pulmonary tuberculosis is associated with toxaemic or febrile symptoms, the pulmonary ventilation is increased on the average by 50 per cent. (Table I); some of this increase being related to the increased metabolism. When the basal metabolism is normal, the pulmonary ventilation is increased on an average by 20 per cent., and there seems to be ground for the belief that the measurement of the pulmonary ventilation may indicate the degree of functional impairment.

It is to the toxaemic or febrile symptoms that the clinician turns for guidance in the treatment of pulmonary tuberculosis. Unfortunately, the only toxaemic signs which can be measured and recorded with any degree of accuracy concern the pulse, the temperature, and the weight, and with them so many fallacies may intrude that they can be valued only in relation to symptoms to which measurement cannot be applied. If it can be shown that the basal metabolism and the pulmonary ventilation vary directly with the degree of toxaemia, and a simple method can be used in measuring them, a noteworthy addition is made to the clinician's equipment for recording the progress of a case under treatment. The observations recorded here show that there is a close relationship between the degree of toxaemia and both the basal metabolism and pulmonary ventilation; this relationship is closer than with the pulse-rate or with the temperature, and consequently offers a better guide in treatment and a greater help in prognosis. The morbid changes in the lungs are of course responsible for the toxaemia, and the estimation of the respiratory exchange at intervals shows whether those changes are progressing or retrogressing. In addition it is a delicate method of determining whether a special

form of treatment or a modification of existing treatment is harmful or beneficial.

The average basal metabolic rate in active cases of pulmonary tuberculosis has been shown to be plus 20 per cent. This increase is more than could be expected for the degree of temperature at the time of the estimation and confirms the work of a number of previous investigators on this point. Since such a disturbance is typical of Graves' disease it has been suggested that the thyroid gland is implicated in the increased metabolism of active pulmonary tuberculosis. McBrayer (4) found the basal metabolic rate and the blood-sugar increased in about one-third of his cases of chronic pulmonary tuberculosis, and advanced a theory that the tuberculotoxins disturbed the endocrine balance. Cordier (11) found clinical signs of hyperthyroidism in the majority of his cases of pulmonary tuberculosis which showed an increased basal metabolism, and Lanz (13) found he could divide his cases with increased basal metabolism into those without and those with symptoms of hyperthyroidism, the increase in metabolic rate in the latter being greater than would be expected in a similar type of case without symptoms of Graves' disease. He also points out that in healed or early lesions an increased basal metabolic rate may be found which is entirely due to hyperthyroidism and has no relation to tuberculosis. Evidence of thyroid disturbance in pulmonary tuberculosis has been found by Berg (23). He found that the sugar tolerance curve rose to values at the upper limit or just above normal (average maximum 0·195 per cent.) and that the curve was prolonged. The deviation from normal was more marked according to the activity of the case and approached the normal as the patient improved. Cases with altered blood-sugar reactions showed symptoms of hyperthyroidism in a larger percentage than other cases. He rules out pyrexia as a cause of hyperthyroidism and suggests that a toxic action on the liver may be one of the causes.

Pierson (24) has suggested that the thyroid or several endocrine glands, are involved in the ability of an individual, or a family to resist tuberculosis, and a similar view is held by Obermer (25), who believes that ' the endocrines hold the key position in the mechanism of resistance to all infection ' and that ' from the " endocrine " point of view the successful resistance to a tuberculous invasion is dependent upon well-balanced, healthy, and vigorous ductless glands '. He has investigated a number of cases of pulmonary tuberculosis by examining the end products of metabolism, and his results confirm the view that the metabolism is increased in active pulmonary tuberculosis.

There appear to be three views with regard to the relationship between pulmonary tuberculosis and hyperthyroidism. 1. That the toxic products of the tuberculous processes stimulate the thyroid. 2. That there is no direct relation between the two, but that their occurrence together is a mere coincidence. 3. That the state of the endocrine glands determines the type of the tuberculous lesion, or, in other words, governs the resistance.

It would be unprofitable to discuss these more fully since we have insuffi-

cient data and there are many difficulties in the way of arriving at a definite decision. The question is, however, one which deserves investigation.

From a clinical point of view the value of a particular method of investigation is judged by the help it can give in diagnosis, prognosis, or treatment. All the cases used in the present investigation had reached a stage at which diagnosis presented no difficulty. Early, and doubtful cases, and those in the terminal stage with marked pyrexia and toxaemia were not examined; attention has been confined chiefly to the intermediate stages. Variations from the normal have been most noticeable in (1) the basal metabolism, (2) the pulmonary ventilation, and (3) the percentage of carbon dioxide in the expired air. The information to be derived from each of these methods of investigation is slightly different. It has been discussed under the respective headings.

Prognosis depends on the activity of the tuberculous process, and I have endeavoured to show that increased metabolic rate indicates activity even in the absence of rise of temperature and pulse-rate, i. e. in apyrexial fever.

With regard to treatment I believe that periodical determinations of the pulmonary ventilation and basal metabolic rate are of considerable value in regulating the degree of exercise a patient is capable of performing.

Conclusions.

1. In active pulmonary tuberculosis the basal metabolic rate is slightly increased (average plus 20 per cent.). This increase may occur with a normal temperature.

2. With certain exceptions (inanition, cachexia), the more severe the disease the higher is the basal metabolic rate.

3. In cases of pulmonary tuberculosis where fibrosis is taking place, the basal metabolic rate is within normal limits.

4. The pulmonary ventilation is increased in pulmonary tuberculosis.

5. The pulmonary ventilation varies directly with the basal metabolic rate, and either can be used in following the progress of a case.

6. Rest influences the basal metabolism and pulmonary ventilation favourably. It is suggested that diminution in pulmonary ventilation is an important factor in the treatment of pulmonary tuberculosis.

7. The pulmonary ventilation may be increased when the metabolism is normal.

8. The percentage of carbon dioxide in the expired air is less than normal in chronic pulmonary tuberculosis, the more extensive the disease the greater is the deviation from normal.

9. The respiratory quotient is lowered slightly in cases of long duration.

10. Observations on the respiratory exchange in pulmonary tuberculosis give information with regard to the activity of the disease and repeated examinations provide an index as to progress.

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A STUDY OF SO-CALLED LIPOID NEPHROSIS [1]

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RECENTLY much has been written, particularly in Germany and America, concerning an affection which has been separated from the nephrites and is called nephrosis. This name was first used by Müller (103) (1905) as a purely pathological distinction between degenerative and inflammatory parenchymatous kidney change. Others, particularly Munk (106) (1913), Volbard and Fahr (141) (1914), Epstein (39) (1917) adopted it and attempted to define a corresponding clinical distinction between these two forms of renal change. But the distinction between nephritis and nephrosis has failed, and observers now talk of nephritis with superimposed nephrosis and nephrosis with superimposed nephritis.

Subacute parenchymatous nephritis or 'large white kidney' is associated with profound metabolic changes, indicated by lowered basal metabolism, disturbance of the plasma proteins, and changes in the cholesterol distribution almost unparalleled in any other disease. Generally, haematuria is present at the onset, later, interstitial changes and fibrosis occur leading to uraemia. Occasionally haematuria has not been detected, and the renal change may persist in the purely parenchymatous form which the German authors mentioned consider to be degenerative. Now this condition is sometimes clinically indistinguishable from amyloid disease of the kidney and from syphilitic kidneys, and in these last we have a typical picture of pure nephrosis.

In this disease a large percentage of cholesterol in ester form is found in the kidney, and still higher figures are found in the so-called myelin kidney, of which examples have been described by Lorrain-Smith (94) (1911), McNee (101) (1922), Parkes-Weber (146) (1923). This richness in cholesterol ester has resulted in the name 'Lipoid Nephrosis' for all cases in which renal parenchymatous change is, at some time or another, associated with disturbance of cholesterol distribution and metabolism. Examples of lipoid nephrosis in pure or complicated forms have been described by Volhard and Fahr (141) (1914), Munk (107) 1916), Epstein (39) (1917), Epstein and Lande (40) (1922), Rabinowitz and Childs (116) (1923), Dyke (32) (1924), Major and Hellwig (96) (1925), Clausen (28) (1925), Karger and Ullmann (81) (1925), Mason (97) (1926), Murphy and Warfield (108) (1926). The discussions of Fahr (42), Kollert (85), Bennett, Davies, and Dodds (11), Bennett (12), and Elwyn (35) are also to be noted.

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The early stages of the disease are almost indistinguishable from acute nephritis, and only when the oedema and the albuminuria have persisted for many weeks may suspicions arise that a so-called ' nephrotic ' process is present. Different authors lay stress on different factors as diagnostic. Munk stresses the oedema, albuminuria, and the presence of doubly refracting bodies in the urine; Epstein, the metabolic changes; Volhard and Fahr, the absence of both haematuria and anaemia. In my studies I have used as criteria the hypercholesterolaemia and low basal metabolic rate, as these were universally present in cases which might be described as nephrosis or as having the nephrotic element (Nephrotische Einschlag). Volhard and Fahr consider that in pure nephrosis haematuria does not occur, and if this criterion is essential I am unable to identify such cases and ought to consider all my cases as a mixture of nephritis and nephrosis, however closely the clinical picture resembles in other respects the description of pure nephrosis, e. g. Cases 1 and 5. However, in the healing of acute nephritis, the haematuria disappears before the albuminuria, and the occurrence of early haematuria might easily be missed. Consequently the absence of haematuria cannot be regarded as a reliable criterion.

Subacute or chronic parenchymatous nephritis runs a variable course— from months to years. The rapid cases either terminate in uraemia or from acute infections, generally pneumococcal or streptococcal; the more chronic show a variable degree of anasarca, but later, with the onset of sclerotic changes in the kidney this symptom disappears, cardiovascular changes occur, and the time comes when the patient may feel he has recovered; but the disease progresses to fatal uraemia. Case 4 is an example of the rapid form and Case 10 of the chronic. The sclerotic process occasionally does not seem to occur and the patient has recurrent oedema for many years, e. g. Case 5. These cases with a prolonged benign course might appear to form a separate group corresponding to the pure nephrosis of Munk, Epstein, &c. Of my patients I could only definitely place in this group Cases 2 and 5. Authors who believe that this group is a separate entity consider the prognosis as good, but though my experience is limited, I doubt if this is so. Case 5, for example, left hospital in 1924, there were no real signs of recurrence till 1927, and in the interval might easily have been considered as having recovered. Clearly the clinical condition can persist for many years without any cardiovascular change or nitrogen retention. Cases 2 and 5, having complete absence of such changes for five and eight years respectively, should be considered as examples of nephrosis, and yet both had haematuria at the onset of the illness.

The cases of Dyke (32) and of Major and Hellwig (96) showed some glomerular degenerative change, and Elwyn (35) believes that so-called pure nephrosis is always preceded by a glomerulo-tubular nephritis, and hence he cannot see any justification for regarding a later stage (of ' nephrotic ' type) as a separate entity. Murphy and Warfield (108), who follow the German authors closely, consider that Elwyn does not face the facts. Bennett's (12) views are similar. As a result of the study of my cases I agree with Elwyn and think

that, on clinical grounds alone, particularly the complete gradation between nephrosis and mixed nephritis and nephrosis, there is no justification for this subdivision of parenchymatous nephritis.

Case 21, with typical symptoms, appears to belong to the group of syphilitic kidneys described by Rose Bradford (20) as a secondary manifestation of syphilis, these cases have a benign course and tend to recover. It corresponds to Munk's syphilitic nephrosis. Here, as in amyloid nephrosis, the cause is clear, and though subacute parenchymatous nephritis closely resembles these cases the cause of it is different.

This disease can be considered under the following headings: 1. (a) Albuminuria; (b) Alteration in plasma proteins. 2. Alteration of cholesterol metabolism and distribution. 3. Lowered basal metabolism. 4. Anaemia. 5. Oedema.

1. *Albuminuria and Plasma Protein Changes.*

In parenchymatous nephritis albuminuria is very considerable. German and American authors maintain that in pure nephrosis there is no glomerular change, and Fahr (42) considers the proteinuria to be an exudation from the necrotic tubules. However, the work of Adami (1), Ribbert (117), Posner (114), and Seelig (126) has demonstrated the probability that albuminuria is of glomerular origin, consequently it is difficult to believe that there is no glomerular change in so-called nephrosis. The glomeruli, according to Cushny (30), act as filters which allow to pass a non-protein filtrate similar in composition to a plasma from which the proteins have been removed (also Wearn and Richards (145)). It would surely be wrong to assume that a change of capillary permeability, such as would allow of albuminuria, must necessarily be accompanied by microscopically visible change in the glomeruli. We are perhaps justified in assuming the probability of such alterations of capillary permeability, for this is influenced by so many factors. Morawitz and Deneke (102) found the skin capillaries to be more permeable than normal in glomerulonephritis, whereas in cardiac oedema they found no change. Schlayer and Takayasu (125) demonstrated that functionally deranged glomeruli did not necessarily show visible change.

If the argument, that the occurrence of proteinuria denotes glomerular change is sound, we can no longer look upon nephrosis as an affection of the tubules only. Of course, the glomerular change might be considered a sequel of the tubular injury, but Fahr (42) prefers to consider the albuminuria as arising from the tubules. He states:

'Normalweise halt jede Körperzelle das Eiweiss zurück und bei degenerativ-entzündlichen Veränderungen irgendeines Gewebsabschnittes, bei Kappillarschädigung durch Stauung usw. werden alle Körperzellen für Eiweiss durchlässig, d. h., es tritt aus den Gefässen Eiweisshaltige Flüssigkeit in die Umgebung.'

This divergence from current opinion as to the origin of albumin in the urine

needs support from further investigation.   Hewitt (75) has shown that urinary albumin is probably identical with serum albumin, which is not surprising if albuminuria is a result of altered capillary permeability.

Besides the albuminuria there is also a disturbance of the body proteins. This is manifested by the diminution of the total plasma protein and the reversal of the normal albumin to globulin ratio.   The normal values are as follows :

	Fibrinogen	Albumin	Globulin
Rusznyák (123)	0·13–0·24 %	3·25–4·4 %	1·25–2·1 %
Rowe (121)		4·6–6·7 %	1·2–2·3 %

Similar figures are given by other observers.   In the urine the albumin to globulin ratio is much higher, but the ratio varies considerably.   In nephrosis the fibrinogen is increased four- to eight-fold (100, 123), the albumin is greatly diminished and the globulin increased (Epstein (37), Linder, Lundsgaard and Van Slyke(91), Kollert (86), Rusznyák (123), Foster and Whipple (47), Geill (59).

Though these values may be of clinical use, it is doubtful whether we can yet appreciate the significance of these changes.   The increase of the fibrinogen is undoubted and is possibly greater than in any other disease.   Here we may note the obviously increased sedimentation rate of the red cells in this disease —and which is probably correlated with the increased fibrinogen content of the blood (44).   As regards the other protein changes we cannot be quite so certain of the validity of the results because the methods of analysis depend entirely on the separation of the proteins by salting-out procedures (Robertson (119), Howe (78), Cullen and Van Slyke (29), Wu (150), Rowe (121).   Though this is the classical method of separating these proteins, it only affects a rough separation (59), especially as, in most of the methods, the precipitation is done on the undiluted plasma.   A complete separation of the plasma proteins can only be effected by dissolving and reprecipitating the fractions many times, and when we also consider that plasma globulin has been divided into four or more separate globulins (Howe (78,) Stern (132)), and plasma albumin also into a number of fractions (Oppenheimer (111)), it becomes difficult to formulate hypotheses from the results of our rough analytical methods, even though the results may be more or less concordant.   It is not inconceivable that other abnormalities of the plasma, e. g. a high cholesterol content, may alter the precipitability of different protein fractions, and we know that there is a close association between cholesterol and the plasma proteins in different degrees.

These plasma protein changes form the basis of the theories concerning the nature of nephrosis.   Kollert (85) considers the disease to be a widespread affection of all the body cells, the breakdown of which results in an abnormal production of plasma proteins.   He bases his idea on the hypothesis of Hertzfeld and Klinger (72) that the serum proteins consist of an interrelated series of colloidal particles of different degrees of dispersion, and that fibrinogen is the parent and largest molecule and that globulin and albumin are next produced, in that order, by hydrolysis.   The same agent that causes this widespread

change also affects the kidney epithelium. Munk also talks of disturbance of
the general colloid metabolism of the body and considers some experiments
on the interchangeability of albumin and globulin as suggestive in this con-
nexion.

However interesting such speculation may be, we know very little about
the origin of plasma proteins and their state of existence in the plasma. Do they
exist separately (72)? are they very labile bodies? or parts of a complex unit?
(Hardy (69), Sorensen (129).

It seems probable that the continued drain of protein from the blood is of
importance, for these bodies apparently have a conservative metabolism.
Whipple and his co-workers (47, 128), have shown that, after the removal of
plasma proteins in the living animal, regeneration is quick at first within limits,
probably from reserve supplies, but that complete regeneration is a more
difficult and relatively lengthy process. The observations of Hiller, McIntosh
and Van Slyke (77) show that in cases of glomerulo-nephritis the albumin to
globulin ratio in the urine is about 5, and this value increases as these cases
approach the type of so-called pure nephrosis when the ratio exceeds 10. Con-
sequently, as the protein loss through the kidney in 'nephrosis' is mostly
albumin, it seems probable that the characteristic changes in the plasma proteins
are secondary to the albuminuria. It is probable that the abnormal plasma
which circulates in this condition might lead to widespread body changes. It
is, however, surprising that the albumin globulin ratio in the urine in amyloid
nephrosis should be exceedingly low (77).

2. *The Disturbance of Cholesterol Metabolism and Distribution.*

A. *The kidneys.* Kaiserling and Orgler (80) (1902), made the first observa-
tions on the presence of doubly refracting bodies in the kidneys and in the
urine. These bodies were identified by Panzer (112) and Adami and Aschoff
(2) as containing cholesterol in ester form. Though examination with the
polarization microscope gives a rough idea of the amount of ester cholesterol in
the kidney, it can be determined accurately only by chemical analysis.
Windaus (149), Lapworth (90), Beumer (15), and Fex (45) have reported
analyses. The normal amount of cholesterol in the fresh kidney is given by
Windaus as

        free cholesterol   .   .   .   . 0·22 per cent.
        ester cholesterol .   .   .   . 0·01 per cent.—0·03 per cent.

and in large white kidneys as

        free cholesterol   .   .   .   . 0·22 per cent.—0·33 per cent.
        ester cholesterol .   .   .   . 0·09 per cent.—0·65 per cent.

Fex obtained similar results, showing that in cases of glomerulo-nephritis
and of 'nephrosis' the free cholesterol was hardly if at all increased, but the
bound cholesterol was greatly increased. Sometimes this increase of cholesterol

ester (and also of other 'lipoids') gives the kidney a peculiar macroscopic appearance—the so-called myelin kidneys, but this is not necessarily present in kidneys of which the ester cholesterol content is very high. Fex also showed that the chemical estimation of cholesterol esters corresponded in a rough way to the polarizing microscope findings. The doubly refracting bodies are found mostly in the cells of the tubules but, in some cases, in the interstitial tissue, in so-called foamy cells, and are supposed to get into the interstitium secondarily, as if it were a process of removal from the cells of the tubules (Lohlein (93) and Wail (144). According to Fex the cholesterol content of the liver and supra-renals in these cases was normal.

In two of our cases we estimated the cholesterol content of the kidney. The kidneys of Case 15 showed advanced chronic glomerulo-nephritis with fibrosis. *Though the blood cholesterol was normal*, the kidney was abnormally rich in ester.

The analysis gave

> free cholesterol . . . . . 0·27 per cent.
> ester cholesterol . . . . . 0·20 per cent.

In Case 5 high hypercholesterolaemia had been noted a few months before death.

The kidney contained

> free cholesterol . . . . . 0·39 per cent.
> ester cholesterol . . . . . 0·36 per cent.

In this case other organs analysed as to their cholesterol content gave the following results :

	Amount of Cholesterol as percentage of dry substance		Amount of Cholesterol as percentage of moist substance	
	Free	Ester	Free	Ester
Liver	1·028	0·161	0·227	0·036
Lung	1·756	0·199	0·269	0·030
Spleen	1·288	0·316	0·239	0·069
Gall-bladder bile	—	—	0·175	0·065

These results are approximately within normal limits.

B. *The blood.* In almost all cases of subacute or chronic parenchymatous nephritis there is an increase in the cholesterol content of the plasma, affecting either the free or ester cholesterol, but more usually both. This increase appears early in the disease; in Case 4 definite hypercholesterolaemia was found eight weeks from the onset. Increases in the *total* cholesterol content of the blood or plasma have been noted by Chauffard (26, 27) and other French workers (147, 148), Klinkert (83), Bacmeister and Henes (7), Henes (71), Port (113), Stepp (131), Strauss and Schubardt (133), Hahn and Wolff (64), Maxwell, and others. My results are in the appended table.

Cholesterol in the plasma is present in both free and ester form and in corpuscles almost entirely in the free form. Richter-Quittner (118) considered that plasma contained cholesterol in ester form only, but if the corpuscles were injured by certain anticoagulants, free cholesterol passed into the plasma.

Gardner and I (54) could not confirm this. The cholesterol content of the corpuscles seems to be fairly constant and unaffected by differing conditions of health. This was shown by direct analyses in different cases, but the isolation of pure corpuscles, quite free from plasma, is too full of difficulties for routine use. Observers, who estimate the corpuscular content of cholesterol indirectly from analyses of whole blood and plasma, find variations in the sterol content of the red cells under certain conditions, but it is difficult to place reliance on results which depend on estimation of corpuscular mass by haematocrit methods and in which the errors tend to accumulate in the indirect determination. By using plasma instead of whole blood for our analyses we avoid including the constant corpuscular free cholesterol which masks changes in the relative amount of free and ester cholesterol in the plasma, and we also avoid the less recognizable effects of the presence of anaemia.

Most observers assume that there is a normal value of the amount of cholesterol in the plasma, but give different figures for this according to the analytical method used, and, as a rule, quote only small limits of variation. Gardner and I used the digitonin method of estimation (54), which has the advantages of accuracy and of allowing the separate and direct determination of the free and bound cholesterol while not having the inaccuracies of the colorimetric methods generally used (Gardner and Williams (52), Gardner and Fox (50)). The chief disadvantage is that 10 to 20 c.c. of blood are needed for an estimation. In a recent paper Gardner and I (54) discussed the cholesterol content of the plasma of healthy individuals of both sexes and found that the variations were so large as to render average figures almost meaningless. It follows from this that states of hypercholesterolaemia cannot be assumed to exist unless the cholesterol content of the plasma is either definitely outside the normal limits of variation or is higher than the known normal value in a given individual. In cases of 'nephrosis' it is justifiable to speak of hypercholesterolaemia, for the plasma sterol is extraordinarily increased. Our normal limits for *total* cholesterol in plasma were 0·078 per cent. to 0·227 per cent., with corresponding variations of the free and ester portions, whereas in some cases of 'nephrosis' values of over 0·5 per cent. occur.

We do not as yet understand the roles of the free and bound fractions of the plasma cholesterol, so we have thought it important always to estimate the fractions separately. In normal plasma the ratio of free to ester is generally approximately 1:2, but occasionally we find very low values for either fraction, even in health. Free cholesterol seems to be the more stable portion, while the ester cholesterol seems more liable to undergo changes in normal conditions (Aschoff (4), Fex (45)). In an individual in whom we studied the effect of different feeding over prolonged periods it appeared that the level of the ester cholesterol in the plasma was much more dependent than the free cholesterol on the intake of sterol with the food. The question is complicated, for a rich fatty but otherwise normal diet containing about 0·8 grm. of cholesterol a day had more effect on the plasma cholesterol than feeding with brains, with a cholesterol

intake of 3·6 grm. a day. This effect is possibly due to the better absorption of the sterol in ordinary food by the intestine (56). In some other as yet unpublished work we have obtained evidence of independent functions of the free and ester forms of cholesterol in a study of cholelithiasis, and also in the effect of administration of certain bile acids in a case of cholelithiasis where the ester cholesterol was almost absent in the plasma before the treatment. Further evidence of the different roles of the two fractions is to be found in the distribution of cholesterol in the body in health and disease: in health the presence of free cholesterol only in the brain, bile, and red-blood corpuscles, and in disease the increase of tissue cholesterol affecting only, or mainly, the ester form. The importance of separate determinations of free and ester cholesterol is further suggested by the findings of Gardner and myself in a study of the cholesterol content of the plasma in pregnancy (57), where the relative amounts of the two forms of cholesterol undergo remarkable cyclical change. It would be quite impossible to assess, for example, analyses of the blood cholesterol in the toxaemias of pregnancy, such as those reported by Maxwell (98), without consideration of this phenomenon.[2]

In most of my cases analyses show a ratio of free to ester cholesterol in the plasma more or less within normal limits, but occasionally either the free or ester is present in preponderating amount. In Case 11, in which vascular changes were marked, free cholesterol was 0·473 per cent., the nearest figure to this being 0·278 per cent. in Case 2, in which the vascular changes were absent. Disproportionally high values of 'ester' were found in Case 5 of 0·499 per cent., after thyroxin administration, in Case 7 of 0·694 per cent. immediately after a period of thyroid medication, and a high value in Case 2 of 0·429 per cent. but with a proportionally high 'free'.

Hypercholesterolaemia can be very persistent, and in Case 5 was still present after nearly four years. This increase of cholesterol in the plasma persists for as long as there is *any tendency* to oedema, but after this we find normal values of plasma cholesterol. When this has occurred, nitrogen retention and cardio-vascular changes appear, and the patient is liable to uraemia. This is shown in Cases 10 and 12, in which the last cholesterol determination was within normal limits but the blood-pressure and blood-urea were increased. But even then the plasma cholesterol may remain high; Case 9 at the present

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[2] An example of this is the following plasma analysis from a case of albuminuria of pregnancy in which the pregnancy was terminated in the thirty-fourth week. Increased blood-pressure and albuminuria retinitis were present.

Date	14.12.28	14.1.29	8.2.29
Weeks of pregnancy	34	(38)	
Free cholesterol. g. %	0·143	0·189	0·082
Ester cholesterol. g. %	0·187	0·134	0·163
Total cholesterol. g. %	0·330	0·323	0·245

The figures for what would have been the thirty-eighth week show a very considerable increase in the absolute and relative amounts of free cholesterol, such as is not present normally at that period.

moment has a high blood-pressure and is recovering from albuminuric retinitis, and yet the blood cholesterol is still high. Clearly, the fall of the plasma cholesterol value is not due, or at any rate not entirely due, to the sclerotic processes, nevertheless it can be stated that the hypercholesterolaemia diminishes about the time when definite clinical signs of contraction of the kidney appear. These results agree with the observations of Henes (71), Epstein and Rothschild (41).

C. *The urine cholesterol.* Normally, cholesterol is present in minute quantities in the urine, as was demonstrated by Bacmeister and Havers (6), Pribram (115), and Gérard (61). In renal cases doubly refracting bodies have been observed in the urine by Kaiserling and Orgler (80) and Munk (104), and cholesterol was detected in these cases by Gross (63), using chemical methods. Munk lays great stress on the presence of doubly refracting ' lipoid ' bodies in the urine and thinks them of diagnostic importance in the differentiation of true ' nephrosis ' both from acute and toxic nephritis, the result of mercury or salvarsan poisoning. This view is opposed by Finger and Kollert (46), Knack (84), Genck (60), and Barat (10). Gardner and I (53) analysed a number of urines, having first of all determined the amount present in normal urine. In our experiments we used carefully filtered urine to avoid the presence of cell debris. We found that normally 1·7 to 4·0 mg. of cholesterol were excreted per day, partly in free and ester forms but also in another form which could only be estimated after vigorous acid hydrolysis. We suggested that this cholesterol was in the form of an ethereal sulphate, but we have been unable so far to confirm this despite many efforts to isolate this fraction.

We estimated the cholesterol in the urine in nephritic cases, and our results were as follows :

| | | Cholesterol per day in mgs. | | |
Case.	Presence of Hypercholesterolaemia	Free and ester	Hydrolysable by acid	Total
10	Present	28·3	12·5	40·8
12	Present	30·14	11·03	41·17
		1·05	15·03	16·08
7	Present	10·8	22·9	33·7
		8·92	8·24	17·16
14	Absent	0·96	1·29	2·25
20	Absent	0·74	0·26	1·0

In Case 7 we estimated also the cholesterol precipitated with the protein on boiling, and also the cholesterol in the protein free filtrate, with the following results :

| | Mgs. per day of Cholesterol in : | |
	Coagulated Protein	Protein free Filtrate
Free cholesterol	3·26	0·528
Ester cholesterol	4·96	0·176
Cholesterol obtained after acid hydrolysis	—	8·24
Total all forms	8·22	8·944

The precipitation of the bulk of the free and ester cholesterol with the protein is noteworthy. In plasma, cholesterol appears to exist in close associa-

tion with euglobulin (Bang (9), Handovsky (65, 66), and co-workers (17, 18, 67, 68), Theorrel (136), Frankenthal (49)). Gardner and I (55) showed that not only was the cholesterol precipitated with the proteins by salting out (the euglobulin fraction showing the greatest attraction for the sterol), but also that the cholesterol could not be completely separated from the proteins even after a process of purification by solution and precipitation repeated seven times. This result we also obtained with urine from a case of nephritis. The urine was treated in the same way as the plasma (55). The cholesterol was estimated in the protein fractions and also in the filter papers used. There was insufficient globulin for separation into euglobulin and pseudo-globulin. The results were as follows :

	Weight of Protein per day, in grm.	Cholesterol in mg. per day			Percentage of Total Cholesterol retained by Protein	Amount of Cholesterol retained by 100 grm. of Protein, in grm.
		Free	Ester	Total		
Urine 1						
Albumin	6·65	0·95	1·41	2·36	15·06	0·036
Globulin	0·522	2·55	3·79	6·34	40·6	1·215
Filter paper	—	2·67	4·25	6·92	—	—
Total				15·62		
Urine 2						
Albumin	5·82	0·75	1·41	2·16	25·4	0·037
Globulin	0·47	0·29	0·75	1·04	11·65	0·223
Filter paper	—	4·52	1·21	5·73	—	—
Total				8·93		

These results demonstrate the attraction between the sterols and the proteins in the urine, and, as in plasma, the attraction is most marked as regards the globulin. We will refer to this again later.

Discussion of the Cholesterol Metabolism of Nephritis.

We have seen that in parenchymatous nephritis the sterol in the kidney, plasma, and urine is greatly increased. But we do not know definitely that cholesterol, though the main sterol, is the only one present, for the tissues and blood contain small quantities of other non-saponifiable ether extractable substances. Cholesterin can be synthesized in the body, and there is a close chemical similarity between cholesterol and the bile acids. We know of no intermediary products in the human body between these, nor have any precursors of cholesterol been identified.

The metabolism of cholesterol is both exogenous and endogenous, of the latter we know little, but the former appears to be very conservative, for, under normal conditions, the level of the plasma cholesterol can only be changed very slowly. Certainly the high plasma cholesterol content in this disease cannot be produced by any mode of feeding. In nephritis the cholesterol of the plasma varies in the course of the illness, but it cannot be lowered by restricted diet. In one case (9) feeding for sixteen days on an almost sterol free diet, which

consisted mainly of potato and white of egg, had no effect on the plasma cholesterol. Beumer (13) produced no effect on the plasma cholesterol by feeding on either a sterol rich or a sterol poor diet.

Another aspect to consider is the cholesterol balance between intake and output. Normally, in man, there is an excess of output of sterol in the faeces over the intake with the food. This is small but fairly constant in amount. An experiment made in Case 9 gave the same result—showing that there was no unusual retention of ingested sterol. Beumer (14) obtained this result only when giving a diet poor in fat, if it was rich in fat he found increased retention of cholesterol. Nevertheless, this retention had no effect on the amount of the plasma cholesterol.

Other factors which might have an effect on the plasma cholesterol are the basal metabolic rate and the activities of the liver. Epstein and Lande (40) pointed out a correlation between basal metabolism and the blood cholesterol under different conditions, which Gardner and I (58) were not entirely able to confirm. They maintain that in Graves' disease with a high basal metabolic rate the blood cholesterol is low, but we have not found that the plasma cholesterol in this disease is below normal limits. In myxoedema the low basal metabolism is associated with a high blood cholesterol—this we have confirmed (and also Luden (95)). The inverse proportion between basal metabolism and plasma cholesterol in cases of hypothyroidism is sometimes striking, though not absolutely constant. In myxoedema the giving of thyroid gland or thyroxin produces an increase in the basal metabolic rate and a lowering of the plasma cholesterol. Nothing similar has been observed in our cases of ' nephrosis'. Both Cases 5 and 10 had their maximum values for plasma cholesterol after treatment by thyroid and when their basal metabolism was at its highest. This is perhaps comparable to the results obtained by Gardner (34, 51) with cats and rabbits during inanition, when increases in the blood cholesterol occurred, possibly as a result of the transference of fat from the depots during this state, whereby some cholesterol is liberated from the tissues.

I have suggested the possibility that the liver has an action on the blood cholesterol, and a few experiments have been made. Patients have been given bile acids either in the form of desoxycholic acid orally or of dehydrocholic acid intravenously, which substances have been shown by Neubauer (110) to be powerful cholagogues. In Case 5 there was a considerable following fall in plasma cholesterol, while in Case 9 no such effect ensued. This aspect is worthy of further study.

Evidence as to the relationship between cholesterol metabolism and other metabolic processes is scanty. The metabolism of cholesterol is generally considered to be closely allied to that of fat, largely because cholesterol is extracted from the tissues together with fat when they are treated with ether or other solvents. Apart from the existence of cholesterol in ester form in combination with fatty acids, it seems to have some association with fat in pathological processes, for if fat is deposited in the tissue cells, cholesterol ester is deposited

at the same time or later. Munk believes that such deposits of cholesterol esters result from damage to the cells of such severity that their complete disintegration occurs in contrast to less severe forms of parenchymatous change which are found when neutral fat alone is deposited. On the other hand, we must remember the close association between cholesterol and the plasma proteins, although the significance of this is not understood.

The metabolism of cholesterol seems also to be related to the activity of the reticulo-endothelial system. Gardner's conception of the cholesterol cycle (51) was that the cholesterol liberated by the continuous destruction of erythrocytes was excreted by the liver in the bile and again reabsorbed from the intestine. It now appears that this destruction of red corpuscles takes place in the cells of the reticulo-endothelial system. Further, experiments such as those of Dewey (31) have shown that cholesterol administered intravenously in the form of a colloidal solution is deposited in this system, but I know of no investigation as regards the possible role of the reticulo-endothelial system in nephritis.

Beumer (15) has suggested that the high plasma cholesterol is secondary to the enrichment of the kidney in this substance, but *prima facie* it is not likely that sufficient cholesterol could be absorbed by the blood from the kidneys to keep the plasma cholesterol raised so high. Case 15 throws light on this, for the kidneys were rich in ester cholesterol, whereas the blood cholesterol was low just before death. Some of Fex's cases seem to support this, though Fex (45) did not estimate the blood cholesterol in these cases (see Cases 17 and 19 of Fex). Beumer's hypothesis, in this form, would not account for the increase of the free cholesterol of the blood, the renal increase being mainly in bound cholesterol. There is equally no direct evidence that the deposition of cholesterol is secondary to the high plasma content.

It might be possible to explain the deposition of cholesterol in the kidney in another way. The blood-supply of the glomerular tuft is the sole blood-supply of the corresponding tubule, and if the blood passing through the glomerulus undegoes any abnormal modification, then must the blood-supply of the tubules be also to that extent abnormal. Now the blood passing through the glomeruli in these cases not only loses the normal filtrate, but also a varying amount of protein, chiefly albumin, up to perhaps 20 to 30 grm. per day. The portion of the cholesterol which we have found to be so closely associated with the proteins is a much smaller value in urine proteins than in plasma proteins. Consequently, the loss of proteins at the glomeruli would alter the physico-chemical state of a portion of the plasma cholesterol, and conceivably leave this portion in a condition in which it might be deposited in the tissue in which the altered blood next circulates, i. e. the tubules.

Although this hypothesis also suggests a cause for the disturbance of physico-chemical equilibrium of the plasma, which Munk postulates, it does not account for the hypercholesterolaemia. Cholesterol in the plasma is probably in a state of chemical combination or of colloidal solution, though in fact it is

insoluble in water and cannot easily be brought into colloidal solution containing as much cholesterol as plasma. Even plasma containing as much as 0·5 per cent. of cholesterol may be quite as clear as normal plasma. We must therefore presume that cholesterol is held in solution in the plasma by the proteins, and consequently, with large alterations in the distribution of the different plasma proteins, it is not surprising that changes should occur in the nature of the equilibrium of the plasma cholesterol.

3. *The Basal Metabolism in Nephritis.*

The value of investigating the basal metabolic rate in these cases has been emphasized by Epstein (40). The earliest observations are those of Aub and Du Bois (5), Bowen and Boothby (19), who find the basal metabolic rate diminished in nephritis associated with oedema, whereas other renal conditions associated with vascular and cardiac changes do not have a low metabolic rate, nor do cases of cardiac disease with oedema. Our figures support these statements. In Cases 2, 5, 7, 8, 10, and 12 the consumption of oxygen in the resting condition was either subnormal, or low within the normal limits. Case 9, who might have been expected to have a diminished basal metabolism, was found to have a normal value. In Case 10, who had secondary contraction of the kidney, the metabolism tended to rise.

It is worth noticing in this connexion the observations of Tribe and co-workers (137–139) that in nephritis, produced in rabbits by uranium acetate, the oxygen consumption of the kidneys was much under normal.

Lowering of the basal metabolic rate was not observed in the other varieties of renal disease.

4. *The Anaemia.*

This has been studied by Brown and Roth (21) in an important contribution, but although their conclusions were largely negative, they are in agreement with those of Linder, Lundsgaard, and Van Slyke (91), and of Bock (16) that there is no evidence of hydraemia. Volhard lays stress on the absence of anaemia in pure nephrosis. All my 'nephrotic' cases had an anaemia of secondary type, and all, except Case 9, had a moderate leucocytosis. There was no alteration in the relative distribution of the leucocytes. The significance of the leucocytosis has not yet been determined.

5. *The Oedema.*

The oedema and hypercholesterolaemia are not directly related, for the former may disappear while the latter is constant. In Case 3 the oedema disappeared rapidly (during administration of irradiated ergosterol) while the plasma cholesterol was actually increasing.

Clinical Note.

The cases in the tables and protocols have been placed in order, starting with those most approaching the so-called ' pure nephrosis '; the later cases are those which showed most cardio-vascular change and nitrogen retention.

Case 1 alone made a complete recovery; it was throughout quite typical of nephrosis, except for haematuria at the onset.

Of those still under observation Case 3 is interesting in that, despite his sixty-seven years, his condition has been identical (excepting for haematuria during a few days) with that of pure nephrosis throughout the past six months. Case 9 is difficult of prognosis, for he recovered from the early stages with oedema and hypercholesterolaemia at about the time of onset of high blood-pressure and albuminuric retinitis, which has now almost disappeared, and his blood-pressure is appreciably lower. Is active fibrosis occurring in his kidneys or not?

The fact that most of these cases die, either from uraemia after apparent recovery, or from an acute infection such as peritonitis, makes it very difficult to estimate the value of therapeutic measures. For example, in six cases the kidneys were decapsulated. Of these, four have died ; one case, whose original disease was mild, is alive after eight years, and one case who has been lost sight of, though he had definite signs of contraction of the kidney when last seen. I am of opinion that decapsulation is quite useless.

Five cases had a terminal peritonitis apparently pneumococcal, excepting Case 5, in which the infection was streptococcal. Case 6 had a streptococcal empyema, is still under observation, and seems almost recovered from the nephritis.

General Discussion.

Entia non sunt multiplicanda praeter necessitatem.

In reviewing the opinion of those who believe that ' nephrosis ' is something other than nephritis, we should realize fully the implications of their hypo-thesis.   How much this conception of ' nephrosis ' involves two separate etiological factors is shown by the following quotation from Murphy and Warfield (108):

' Again, in the cases of pure nephrosis, infection may be engrafted so that one sees nephritis with nephrosis and nephrosis with nephritis. When a case of glomerulo-tubular nephritis with blood-cells in the urine shows oedema and marked albuminuria then nephrosis is superimposed. On the contrary, when blood-cells are found in a case thought to be nephrosis and the blood-pressure rises, then nephritis has been added. If one holds to this conception it simplifies to some extent the chaos into which kidney disease has been brought.'

In other words, the simplification consists of a division of the characteristics of Bright's disease into albuminuria and oedema denoting nephrosis on the one hand, and haematuria and increase of blood-pressure denoting nephritis on the other.   Murphy and Warfield state that Elwyn does not face the facts, but do

they·? Especially in their criticism of Dyke's paper, they maintain that of his cases, 103 only is pure nephrosis and 130 and 133 are not pure nephrosis *because of the ages of the patients and the presence of glomerular damage.* Why should Murphy and Warfield state that age and a slightly increased blood-pressure, not unusual for such age, disprove the diagnosis of pure nephrosis? It seems little use inventing a definition of pure nephrosis as necessarily involving absence of glomerular damage when Dyke's cases (particularly 103, which was typical in every respect) did definitely show glomerular change. We should also examine the arguments of Bennett (12) whose conclusions can be expressed as follows:

(*a*) That lipoid nephrosis can exist, though rarely, as a clinical entity independent of nephritis.

(*b*) That the balance of evidence is against hypercholesterolaemia, being an effect of renal change, and that the increase of cholesterol in the kidney may be a cause or a predisposing cause of subsequent renal damage.

(*c*) That in nephrosis there is no clinical evidence of nephritis except albuminuria.

(*d*) That it is difficult to harmonize the localized histological appearance of the kidneys in these cases with the theory that this is a true primary renal disease.

(*e*) That the oedema is largely of extra-renal origin.

As regards (*a*) we have not observed one case of pure lipoid nephrosis in which haematuria has not occurred *at some time,* although in other respects some of our cases have presented all the features of pure nephrosis and an absence of the features said to be indicative of nephritis. We have explained earlier the possible error involved in stating that haematuria has not occurred merely because it has not been detected. Bennett quotes one case (12), and states that he finds no evidence that there was an initial lesion affecting the glomeruli—an argument similar to that of Murphy and Warfield. In view of the work quoted as to the origin of albuminuria and as to the functional changes in the glomeruli unassociated with demonstrable histological change, we do not think that Bennett has adduced any convincing evidence that glomerular change can be excluded in pure nephrosis.

Bennett considers that the balance of evidence is against the view that the hypercholesterolaemia is the effect of the renal damage. Evidence bearing on this is so scanty that the conclusion is unjustifiable. Though we have criticized Beumer's suggestion that the hypercholesterolaemia might be due to the excess of cholesterol in the kidney, we must remember that the hypercholesterolaemia is correlated with damage of the tubules whether this occurs in so-called pure nephrosis or in ordinary acute nephritis of sufficient duration. Beumer considers that the local disease must be the important phenomenon. This correlation is not obvious in the toxaemias of pregnancy, if one accepts Maxwell's figures. Here the question is complicated by the peculiar and characteristic cyclical change in the plasma cholesterol during pregnancy, and also by the fact that in

these toxaemias the renal change is not necessarily diffuse, the patchy distribution of the lesions sometimes leaving much of the kidney normal in appearance.

The evidence that the loading of the kidney with cholesterol ester may lead to other forms of renal change (sclerotic and vascular) is very slender. Bennett, after quoting Scarff (124) on the production of arterial change in rabbits by cholesterol ingestion states, 'we do know that arterial lesions such as atheroma can readily be produced by cholesterol feeding in animals'. A careful survey of all the previous work suggests that caution should be exercised before applying these results to other animals or to man. It has long been known from the work of Ignatowski (79), Starokadomski (130), Stuckey (134, 135), and Chalatow (23) that feeding rabbits with various animal foods, above all yolk of egg, produces intimal changes in the aorta and accumulation of anisotropic fats in the liver and other organs. This led Chalatow and Anitschkow (3, 25) to try the effect of administering cholesterol dissolved in sunflower oil; they produced thereby accumulation of lipoids, chiefly doubly refracting esters in the suprarenal cortex, in the liver, spleen, and lymph glands, and later a deposit in the intima of the aorta, together with hyperplasia of the elastica—similar changes to those of atherosclerosis in man. This work was criticized by Wacker and Hueck (142) because of the use of the stomach tube and the administration of foods to which rabbits are not accustomed. Wacker and Hueck fed rabbits by the mouth with oats mixed with cholesterol and found an increase in the blood compared with normal of both free and ester cholesterol as well as an accumulation of doubly refracting fats in the suprarenals, liver, and other places, and also aortic change of the kind mentioned. They were unable to produce aortic changes in either dogs or cats, though feeding was prolonged for two months. Anitschkow (3) also failed to find arterial change in rats fed with cholesterol for five months. Bailey (8) has repeated these feeding experiments and concludes that the rabbit is unable to cope with large doses of cholesterol. Yuasa (151), under Schönheimer's direction, by very prolonged feeding with diets containing added cholesterol, produced the so-called cholesterin disease (loading of the liver, &c., with cholesterol) in mice, rats, and cats, but in only half of the rats and mice was atherosclerosis observed and in none of the cats. He thinks that these results do not point to any essential difference in principle between the metabolism of the herbivora and the carnivora but that there is a difference in the sensitiveness of the intima of the arteries of different animals towards excess of cholesterol. In all these observations it is tacitly assumed that cholesterol deposition in the arterial intima is identical with the process of the laying down of cholesterol in the liver, suprarenal, and other organs. From Gardner's (33, 51) work on the feeding of rabbits and cats with cholesterol, in as physiological a manner as possible, for periods of about ten to eleven days, it appears that the variations produced in the cholesterol ester content of the liver, at any rate, is hardly pathological; within fairly wide limits it is clearly a physiological process. On the other hand, the deposition of cholesterol in the arteries, when it occurs,

can hardly be considered to be physiological. Yuasa's belief that there is no fundamental difference between the metabolism of the rabbit and the cat is of purely academic interest and throws no light on the possibility of production of atherosclerosis in other animals. In man there is no evidence to associate the occurrence of atherosclerosis with the exogenous cholesterol metabolism.

It is difficult to follow Bennett's argument under (d), as it is not clear what is intended by the expression 'true primary renal disease'. Is the acute nephritis, which is a sequel of an infection such as scarlet fever or tonsillitis, truly primary ? Is the chronic interstitial nephritis which follows lead poisoning truly primary ? All the phenomena of chronic 'nephritis' or of 'nephrosis' can be seen in different degree in acute nephritis—the albuminuria, oedema, hyper-cholesterolaemia, nitrogen retention, high blood-pressure, and visible vascular changes. In refusing to accept the significance given to the name nephrosis, we do not ignore the fact that the causes leading to nephritis or nephrosis may be extra-renal. Clearly, phenomena associated with nephritis or nephrosis may either be produced by the causes that lead to the nephritis or may be secondary to the renal injury. But if we consider, for example, such factors as the oedema and increase of blood-pressure that may occur in acute nephritis which has followed scarlet fever, it is important to note that there is no evidence that these can occur in scarlet fever *unless nephritis is present*. Again, in pyelo-nephritis, following urinary obstruction, or in polycystic kidneys, considerable increase of blood-pressure may ensue, and it is difficult to see why the vascular phenomena should not be considered as a sequel of the renal injury.

It seems to us that the phenomena associated with renal damage are, on available evidence, secondary to the renal injury, though admitting that we have no satisfactory explanation as to how the renal change leads either to disturbance of the cholesterol metabolism or to vascular phenomena.

It is unwise to consider glomeruli and tubules as separate units and to stress isolated changes in one or other structure unless we can definitely corre-late the distant phenomena with separate functional and structural changes in these elements.

It is interesting to consider the evidence from experimental nephritis. In such nephritis most observations have been made on *acute* forms of renal change produced by poisons, and hence the results are not necessarily wholly applicable to chronic nephritis in man. In some work, e. g. that of Frandsen (48), the changes have been chronic. We find that the poisons used can be divided roughly into two groups: those which affect the glomeruli, and those which affect the tubules; but though a poison, such as uranium, may produce an almost purely tubular lesion, its effects are not entirely confined to the tubes. These renal injuries, though histologically similar to renal changes in man, do not necessarily give rise to the same groups of symptoms, e. g. oedema is rarely produced in animals. Frandsen, in his experiments with chronic chromate poisoning, produced a tubular degeneration very similar to 'nephrosis', but the changes in the renal function were not similar to those in man. The nephritis,

at first a degeneration of the tubules, progresses through a process of glomerular involvement to sclerosis. Frandsen thinks that it is impossible to accept the sharp distinction between nephrosis and nephritis, but that both conditions are only different stages or degrees of the same process.

One might here notice the work of Rose (120) using tartrates in the production of artificial nephritis. He obtained an increase of blood cholesterol in an experimental animal poisoned by tartrate by Underhill's (140) method, but actually his control animal showed an almost similar increase of blood cholesterol.

In man the causes of nephritis are often unknown, but toxic causes act in some cases, e. g. lead, mercury, syphilis, tuberculosis and amyloid disease, and also metabolic disturbances, such as are seen in pyloric obstruction (Zeeman, Freedman, and Mann (152), and also Brown, Hartman, Eusterman, and Rowntree (22)). In this report eleven cases of high intestinal obstruction are described in which renal damage ensues apparently from the alkalosis. The pathological changes in the kidney were generally tubular, though occasionally there was more widespread damage. The accompanying clinical phenomena were nitrogen retention, albuminuria, red blood-cells, and casts in the urine, but oedema and vascular changes were absent. The authors did not consider the nitrogen retention as due to the alkalosis but to the renal damage. It is surely impossible here to label these cases either 'nephritis' with superimposed 'nephrosis' or 'nephrosis' with superimposed 'nephritis'. Clearly, histological nephrosis and clinical nephritis had been produced by one common cause.

An extra-renal factor has been assumed to explain the occurrence of renal oedema. It is equally possible that whatever widespread change, such as changes of capillary permeability, or osmotic forces brought about by changes in the composition of the plasma, or other unknown factors, produces the oedema, such change may nevertheless be directly or indirectly caused by the kidney damage. It would be valuable if we knew definitely whether the plasma protein changes are the result of the heavy albuminuria, for the correlation between the osmotic pressure of the plasma colloids and the occurrence of oedema (62, 99) is not to be passed over lightly.

In conclusion we think that so-called 'lipoid nephrosis' is merely a group of symptoms and pathological changes which are part of glomerulo-tubular nephritis. There is no dividing line between pure lipoid nephrosis and nephritis; but it may be allowed as convenient to use the term 'nephrosis' for the syndrome which has been described.

The term 'lipoid' should be omitted altogether as it has no precise chemical meaning.

Conclusions.

1. Subacute or chronic parenchymatous nephritis is marked by an initial stage with oedema and a late stage with cardio-vascular change and nitrogen retention.

2. The initial stage, which may be long or short, is associated with disturbance of the protein and cholesterol distribution in the body and with a lowering of the basal metabolism. There is generally a secondary anaemia and a moderate leucocytosis.

3. In the later stages these characteristics tend to disappear.

4. Rarely, the later stage does not appear to develop.

5. There is no necessity for the conception of 'nephrosis' as a distinctive entity from nephritis.

6. As it is a possibility that the oedema and also the metabolic features of this disease might well be explained by the disturbance of the composition of the plasma following prolonged heavy albuminuria, it is unnecessary to hypothecate unknown extra-renal factors until this possibility has been further explored.

I have to thank my colleagues at St. George's Hospital for their help in allowing me to study their cases. To Mr. J. A. Gardner whose pioneer studies in cholesterol metabolism have been of such importance, I am most deeply indebted for continual encouragement and criticism.

Protocols.

Case 1. Female, aged 16. Five months' illness of pure nephrotic type, except for onset with slight haematuria. Apparently complete recovery ensued, with disappearance of albuminuria.

Case 2. Female, aged 13. Pure nephrotic type for $5\frac{1}{2}$ years, except for onset with haematuria. Fatal termination but without cardio-vascular change.

Case 3. Male, aged 67. Typical nephrosis. No haematuria detected at onset but appeared later in considerable degree for a few days. After eight months, oedema disappeared rapidly during administration of irradiated ergosterol, whereas previous treatment had transient effect only. No nitrogen retention or increase of B. P. Still under observation.

Case 4. Male, aged 19. Eleven weeks' illness terminated by acute peritonitis. Slight haematuria at onset but otherwise typical nephrosis.

Case 5. Female, aged 20. Nephrosis for eight years with long intermissions from oedema. Haematuria detected at major recurrences. Nitrogen retention and slight increase of B. P. only during final few months. Death from streptococcal peritonitis.

Case 6. Male, aged 23. In hospital for ten months. Oedema for six months with moderate increase of B. P., but both these disappeared during treatment of streptococcal interlobar empyema from which he has recovered. Now quite well except for albuminuria.

Case 7. Female, aged 12. Twenty months' illness with fatal termination. Haematuria at onset, anasarca throughout, increase of B. P. during last nine months. Kidneys decapsulated without effect.

Case 8. Female, aged 13. Seven months' illness with anasarca. Haematuria at onset. No nitrogen retention or increase of B. P. Kidneys decapsulated without benefit. Died. P. M. Tuberculosis of lungs. Kidneys large and pale, with yellow stippling of cortex.

Case 9. Male, aged 53. Onset of oedema $2\frac{1}{2}$ years ago. No oliguria, haematuria not detected. After nine months moderate rise of B. P. and arteriosclerotic retinitis observed—this later became definitely renal in type and has now cleared up completely. B. P. not so high as previously, slight albuminuria persists and patient is free from symptoms. Still under observation.

Case 10. Male, aged 14. Anasarca for fourteen months, haematuria not observed at onset. Period of nine months apparent recovery followed, and then termination in uraemia with marked nitrogen retention but only very moderate rise of B. P.

Case 11. Female, aged 15. When seen she had high B. P., albuminuric retinitis and some nitrogen retention. Previously there had been slight oedema during two years. Died at home two months later, probably from uraemia. Note degree of hypercholesterolaemia in sclerotic stage.

Case 12. Male, aged 23. Slight haematuria at onset. Rapid change from anasarcous state to one with nitrogen retention, albuminuric retinitis and high B. P. Death at home after eight months' illness.

Case 13. Male, aged 23. Oedema for nine months. Haematuria at onset. After decapsulation of the kidneys B. P. increased and early retinal change observed. Subsequent history unknown.

Case 14. Male, aged 56. Illness of three months' duration with anasarca. Haematuria at onset. Progressed very rapidly to nitrogen retention, retinitis, increase of B. P. and died in uraemia.

Case 15. Male, aged 35. Admitted to hospital at onset of uraemia from which he died. Eighteen years previously had kidney trouble, with blood and albumin in urine. P. M. atrophic kidneys with diffuse glomerulo-tubular nephritis and advanced sclerosis.

Case 16. Male, aged 64. Typical chronic interstitial nephritis.

Case 17. Male, aged 30. Oedema for four weeks with albuminuria and haematuria but B. P. 200/130. All symptoms cleared up except B. P. which fell to 170/105. Further history unknown.

Case 18. Male, aged 8. Admitted for convulsions, headache, vomiting, albuminuria. B. P. 210/165, albuminuric retinitis. Died a month later in a fit.

Case 19. Male, aged 5?. Typical chronic interstitial nephritis. Wrist drop. History of plumbism.

Case 20. Female, aged 58. Polycystic kidneys. Blood urea 0·33. B. P. 160/100.

Case 21. Male, aged 32. Onset of anasarca fifteen months after contracting lues which was treated with novarsenobenzol. No increase of B. P. but albuminuric retinitis occurred. Eventually completely recovered. Blood cholesterol not estimated.

Blood Counts.

Case No.	Date.	Total Leucocytes.	Polymorphs.	Lymphocytes.	Mononuclears.	Eosinophiles.	Mast.	Red Cells.	Percentage Haemoglobin.
1	23.2.28	14,840	72	25	3	0	0	4,320,000	78
	2.3.28	12,840	63	25	9	3	0	—	—
	29.3.28	9,600	—	—	—	—	—	3,880,000	—
5	12.8.27	13,920	64	28	3	5	0	4,040,000	90
	1.11.27	—	—	—	—	—	—	3,384,000	64
	9.5.28	—	—	—	—	—	—	3,368,000	85
6	20.8.28	16,480	71	26	3	0	0	—	—
7	31.10.24	22,320	61	32	3	4	0	3,296,000	55
8	30.10.25	15,200	—	—	—	—	—	4,248,000	69
9	3.6.25	8,000	55	37	5	3	0	3,944,000	78
	22.6.25	9,920	64	32	3	1	0	4,480,000	78
	26.6.25	6,320	74	21	3	0	2	3,536,000	73
	2.8.25	—	—	—	—	—	—	4,344,000	73
10	4.11.24	15,840	65	28	4	3	0	4,840,000	72
	23.7.25	13,600	—	—	—	—	—	—	—
11	7.8.25	12,000	61	30	6	2	1	3,512,000	54
12	31.10.24	14,000	68	25	6	1	0	2,368,000	46
13	16.1.25	20,160	73	14	7	3	3	4,400,000	74
15	2.12.24	20,960	92	6	2	0	0	1,944,000	35

Case Number.	Sex.	Age.	Date.	Respiratory Quotient.	Basal Metabolic Rate as Percentage difference from Normal.	Percentage Cholesterol in Plasma.			Blood Urea grm. per 100 c.c.	Systolic Blood-pressure in mm. of Hg.	Remarks.
						Free.	Ester.	Total.			
1	F.	16	21.1.28	—	—	0·110	0·263	0·373	—	—	11 weeks after onset. Urine alb. to glob. ratio 21 : 1
			14.2.28	0·95	−11·5	—	—	—	—	—	Syst. B.P. has at no time been higher than 122 mm. No albuminuria at this date
			20.3.28	—	—	0·106	0·116	0·222	—	—	
			4.10.28	—	—	0·055	0·117	0·172	0·033	—	
2	F.	13	26.6.24	0·94	−13·7	0·278	0·080	0·358	—	125	Two years after onset
3	M.	67	21.9.28	—	—	0·113	0·212	0·325	—	110	After rapid elimination of oedema with administration of radiostol
			6.11.28	—	—	0·125	0·246	0·371	0·019	110	
			13.2.29	—	—	0·113	0·211	0·324	—	180	
			6.4.29	—	—	0·133	0·212	0·344	—	120	
			20.4.29	—	—	0·150	0·122	0·272	—	115	
			11.5.29	—	—	0·126	0·250	0·376	—	115	
4	M.	19	7.4.26	—	—	0·160	0·371	0·531	0·027	122	Eight weeks after onset
5	F.	17	28.4.24	0·81	−5·5	0·158	0·122	0·280	—	114	Cholesterol figures are in whole blood
			12.8.27	—	—	0·152	0·293	0·445	—	120	
			25.8.27	0·75	−11·9	—	—	—	—	—	
			14.10.27	—	—	0·154	0·324	0·478	—	145	Had thyroxin 0·4 mg. quot. since 19.10.27
			28.10.27	0·87	+2·2	0·123	0·499	0·627	0·061	125	
			7.11.27	—	—	0·098	0·259	0·357	—	—	Desoxycholic acid administered 2.11.27 to 6.11.27 inclusive
			23.4.28	—	—	0·197	0·229	0·426	0·087	—	
			24.5.28	—	—	0·313	0·173	0·486	0·170	—	
			15.6.28	—	—	—	—	—	0·060	152	Has had a protein-restricted diet
6	M.	23	4.10.28	—	—	0·111	0·202	0·313	—	150	Thyroid gr. iv b.d. 29 Oct.–3 Nov. and thyroxin 0·2 mg. quot. Nov. 3–30
			13.11.28	—	—	0·108	0·231	0·339	0·017	160	
			5.4.29	—	—	0·069	0·065	0·134	—	120	After recovery from empyema

No.	Sex	Age	Date		B.M.R.					Cholesterol	Remarks
7	F.	12	19.4.24	0·93	−29·7	0·154	0·120	0·274	—	120	Cholesterol figures are in whole blood
			5.6.24	0·97	−17·6	—	—	—	—	—	
			7.8.24	0·76	−17·7	0·099	0·694	0·794	—	180	B.M.R. estimated using surface area calculated from figures of 7.1.25
			4.12.24	0·93	−34·2	—	—	—	—	—	
			5.1.25	0·83	−33·7	—	—	—	—	—	
					−25·4						
			7.1.25	0·68	−33·5	—	—	—	—	180	After tapping ascites 8 pints
8	F.	13	10.11.25	0·69	−6·3	0·107	0·141	0·248	—	100	
			14.11.25	0·75	−9·7	—	—	—	—	—	
			3.2.26	—	—	—	—	—	0·082	108	
9	M.	53	21.5.27	—	—	0·190	0·235	0·425	0·032	140	
			3.6.27	0·57	—	—	—	—	—	150	
			9.6.27	0·81	+2·6	—	—	—	—	—	
					−3·7						
			14.6.27	—	—	0·180	0·343	0·523	—	—	Sterol free diet from 7.6.27 to 23.6.27
			23.6.27	—	—	0·165	0·289	0·454	0·029	150	Urea 30 grm. quot. 15.7.27 to 25.7.27 with disappearance of oedema
			26.7.27	—	—	0·181	0·251	0·432	0·074	145	Desoxycholic and dehydrocholic acids administered 27.7.27 to 1.8.27
			2.8.27	—	—	0·134	0·322	0·456	—	—	
			12.8.27	—	—	0·144	0·288	0·428	0·048	170	During previous seven months there was marked albuminuric retinitis, now clearing up
			5.4.28	—	—	0·216	0·068	0·284	—	—	
			9.11.28	—	—	0·144	0·244	0·388	0·033	172	
			22.5.29	—	—	0·091	0·162	0·253	—	—	
10	M.	14	22.4.24	1·07	−19·2	0·242	lost	—	—	155	Cholesterol figures are in whole blood
			27.5.24	1·09	−11·9	0·077	0·211	0·288	—	—	Thyroid administered 24.4.24 to 11.6.24 and from 14.8.24 to 1.10.24
			7.10.24	1·0	−1·1	0·203	0·429	0·632	0·051	160	
			1.11.24	0·86	+1·8	0·137	0·246	0·383	0·056	160	
			25.7.25	0·77	−8·5	0·065	0·107	0·172	0·400	—	
11	F.	15	4.8.25	0·98	−4·7	0·473	0·114	0·587	0·066	230	
			18.8.25	—	—	—	—	—	—	—	
12	M.	23	24.6.24	0·98	−18·5	0·212	0·281	0·493	—	152	
			11.10.24	0·82	−25·4	0·047	0·051	0·098	—	170	
			17.10.24	0·79	−17·5	—	—	—	0·116	—	

Case Number.	Sex.	Age.	Date.	Respiratory Quotient.	Basal Metabolic Rate as Percentage difference from Normal.	Percentage Cholesterol in Plasma.			Blood Urea grm. per 100 c.c.	Systolic Blood pressure in mm. of Hg.	Remarks.
						Free.	Ester.	Total.			
13	M.	24	17.1.25	0·72	+13·2	0·153	0·176	0·329	0·075	170	
			7.3.25	0·80	+17·6	—	—	—	0·164	180	
14	M.	50	10.7.24	1·07	+11·6	0·056	0·091	0·147	0·161	170	
			30.7.24	0·90	−4·1	—	—	—	—	—	
15	M.	35	26.1.24	—	—	0·044	0·066	0·110	0·387	175	
16	M.	64	1.2.26	—	—	0·061	0·073	0·134	0·125	265	
17	M.	30	9.7.24	1·12	+19·6	0·075	0·112	0·187	0·06	180	
18	M.	8	22.5.24	0·88	+3·5	0·128	lost	—	0·450	207	
19	M.	58	7.1.25	—	—	0·070	0·108	0·178	0·155	210	
20	F.	56	11.11.24	0·69	+27·3	0·037	0·065	0·102	0·333	160	

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AN INQUIRY INTO THE FATE OF THYROXIN IN THE TREATMENT OF NEPHROSIS [1]

By ROBERT PLATT

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With Plate 3

THERE is nothing particularly new in the use of thyroid extract for the treatment of renal disease. Percy (1) was probably the first to employ it for this purpose, and recorded a series of cases in 1912. Eppinger (2) studied its effect in certain cases of oedema, but it is Epstein (3) and (7) who in recent years has been the chief exponent of intensive thyroid and thyroxin treatment in the type of case now generally known as chronic nephrosis.

The results of this treatment it is not my present purpose to discuss, but it is the common experience of all who have used the drug that patients with nephrosis exhibit an extraordinary tolerance to thyroxin. Thus about 1 to 1·5 mg. per day is probably the amount of thyroxin required by a theoretically complete myxoedema (4), and an overdose rapidly produces toxic symptoms. Nevertheless, in nephrosis Epstein (3) recommends doses of from 0·1 to 2 grm. of thyroid per day, and has given as much as 20 mg. of *thyroxin* intravenously in a single dose. Large doses, moreover, may be continued over a long period without giving rise to toxic symptoms.

That this tolerance is not accounted for by an extremely low metabolic rate at the commencement of treatment is shown by the fact that only in about 60 per cent. of cases of nephrosis is the basal metabolism below normal (3), and in these it is not often so low as is commonly the case in myxoedema.

There are three other possible ways in which this tolerance might be explained, namely: 1. That the thyroxin is not absorbed. 2. That owing to some chemical or physical change in the blood or other tissues, thyroxin is rapidly destroyed, or its normal action inhibited. 3. That owing to the renal defect, thyroxin is rapidly excreted in the urine, the kidney allowing it to leak through, in the same way as it allows the passage of protein.

The first hypothesis must be laid aside since thyroxin introduced intravenously is as well tolerated as that taken orally. With regard to the second, Epstein and Lande (5) have shown that there is in general a reciprocal relation between the amount of the blood cholesterol and the degree of thyroid activity.

There are, however, a number of exceptions to the rule, and it seems most likely that it merely represents the rate of combustion of available lipoid.   These authors discuss this possibility, but consider that their figures warrant more far-reaching conclusions.   Epstein (3), in fact, believes that symptoms of thyroxin overdose will not occur in nephrosis so long as the blood cholesterol is raised. Even if this be the case, it is not necessarily proof that it is the blood lipoids which are inhibiting the action of thyroxin, but may simply mean that the thyroxin, having failed to act, has also failed to stimulate the combustion of lipoid.

That the tolerance is not dependent simply on the high blood cholesterol is suggested also by a patient recently observed by the author (W. G., see Appendix I) the course of whose illness resembled very closely that of chronic nephrosis except for the frequent presence of blood and casts in the urine, a somewhat raised blood non-protein nitrogen, and a consistently normal blood cholesterol.   Though he was not given thyroxin in enormous quantities, he showed a striking tolerance to the amounts administered.   He received, in fact, 2·4 mg. of thyroxin per day continuously for three months, at the end of which time his pulse-rate had not increased, and his basal metabolic rate was −16 per cent.

In the present incomplete state of our knowledge, both of the metabolic changes in nephrosis and of the normal action of thyroxin, further discussion on how this action might be inhibited is not likely to be fertile.   The suggestion of Kendall (6), however, that thyroxin is an intermediate product which has to be changed into some other form before becoming physiologically active, may in time shed further light upon the subject.

With regard to the third possible explanation of the tolerance, namely that the nephrotic kidney allows rapid excretion of thyroxin to take place, the following experiments were performed.[2]   A number of tadpoles was selected so as to be approximately the same size and stage of development, and divided into groups.   To the vessels containing group ' A ', urine from R. W.,[3] a typical case of nephrosis, receiving 7–10 mg. of thyroxin per day, was added.   To group ' B ' the same amount of normal urine was added, in which had been dissolved thyroxin in the calculated concentration which urine R. W. would have contained had the drug been excreted.   To group ' C ', thyroxin only was administered (positive control), and to group ' D ' normal urine only (negative control).

The thyroxin administered both to the patient and the tadpoles was B.D.H. synthetic thyroxin.   Details of the experiments are given in Appendix II.

Plate 3, Fig. 1, shows three representative tadpoles at the commencement of the experiment, Plate 3, Figs. 2 and 3, show tadpoles from groups A, B, C, and D, one week later.   B and C had died that morning.   All other photographs are taken under chloroform anaesthesia.   Except for slightly increased development of the hind-limbs, A and D have scarcely altered in the course of the week.   In B, metamorphosis is obviously taking place, as shown by the frog-like shape of the body, greater development of hind-limbs, and shortening of the tail. In C, the changes are well advanced, one of the fore-limbs having appeared.

[2] For details see Appendix II.   [3] See Appendix I.

The result would seem to prove beyond doubt that nothing approaching the amount of thyroxin administered is being excreted by the patient in an unchanged condition.

At a later date, two further experiments were started, the tadpoles used being at the same stage of development as group A had now attained. 'E' received very small doses of thyroxin in normal urine, in order to show the sensitiveness of the method, and that not even a small fraction of the thyroxin administered to the patient was being excreted. 'F' received somewhat larger doses dissolved in the urine of an albuminuric patient (W. G.) who had shown thyroxin tolerance, but was no longer receiving the drug. This was intended to show whether the urine of such patients contained any inhibitory substance. In the photographs (Plate 3, Fig. 4) taken after a little more than a week of treatment, both E and F are considerably more advanced in development than A, thus demonstrating that even small amounts of thyroxin appearing in the urine of a nephrotic patient would be detectable by the method employed.

Summary and Conclusions.

1. It is a well-known fact that patients suffering from chronic nephrosis exhibit an extraordinary tolerance to thyroxin, whether administered orally or intravenously.

2. Experiments are described which in the author's opinion demonstrate that this is not due to rapid excretion of thyroxin by the kidney.

3. It is therefore presumed that thyroxin is either rapidly destroyed in the body, or its action inhibited, but it is suggested that such an inhibition does not depend upon the increased level of the blood cholesterol which is commonly found in these cases.

Appendix I. Description of Cases.

1. R. W., male, aged 16, first noticed swelling of the ankles in May 1928. This increased, and the swelling was soon noticed in the face, legs, abdomen, and arms. He was treated at home and in a nursing home, chiefly on high protein diet and oral thyroxin, until April 25, 1929 when he was admitted to the Royal Infirmary, Sheffield, under Dr. Barnes. His condition was then as follows:

Appearance typically waxy; no retinitis; nasal polypi (L) and inflammation of R. turbinal; oedema of arms and back; no pleural effusion; heart normal, blood-pressure 135/70; ascites; marked oedema of abdominal wall; enormous oedema of legs. Urine contained albumin 7·5–15 grm. per litre, globulin in traces only, no blood, no casts. Average amount of urine per day on admission 30–35 oz. During time of experiment on thyroxin excretion—52 oz.

Treatment consisted in high protein and low fat diet, oral thyroxin, intravenous salyrgan, removal of nasal polypi, &c. A record of thyroxin treatment, blood tests, &c. is given below.

2. W. G., male, aged 18, admitted to the Royal Infirmary, Sheffield under Dr. Yates, Nov. 23, 1928. For five weeks he had noted that the urine was occasionally red in colour, and for four weeks he had had swelling of the face, feet, and ankles, which had persisted.

Condition on admission. Pallor; slight oedema of face; no retinitis; heart slightly enlarged, apex in fourth space, blood-pressure 140/90; bilateral pleural effusion; marked ascites; oedema of legs. Urine contained albumin (about 12 grm. per litre) blood on frequent occasions, and large numbers of casts, chiefly epithelial. Average amount of urine on admission 30 oz. per day, later 50–60 oz.

Case 1. R. W.

Date.	Thyroxin mg./day.	Basal Metabolism.	Pulse-rate.	Non-protein Nitrogen mg./100 c.c.	Plasma Protein %.	Cholesterol %.	Remarks.
				Blood.			
13.6.28	—	—	—	30·8	—	0·39	
8.8.28	—	—	—	34·4	—	0·26	
25.4.29	0	—	80–90	44·2	4·7	0·20	
3.5.29	3	—	80–90	—	—	—	
5.5.29	3	—	90	—	—	—	
6.5.29	14	—	90	—	—	—	
15.5.29	14	—	100	41·6	4·4	0·17	
22.5.29	14	—	120	—	—	—	Pyrexia
23.5.29	7	—	—	—	—	—	
1.6.29	7	—	100–110	—	—	—	
16.6.29	7	—	90–100	—	—	—	
17.6.29	10	—	90 100	—	—	—	
24.6.29	10	−35 %	90–100	44·4	4·7	0·18	Oedema throughout

Case 2. W. G.

Date.	Thyroxin mg./day.	Basal Metabolism.	Pulse-rate.	Non-protein Nitrogen mg./100 c.c.	Plasma Protein %.	Cholesterol %.	Remarks.
29.11.28	Thyr. ext. gr. vi	—	70–80	53·0	5·1	0·16	
13.12.28	gr. ix	—	90	44·0	—	—	
24.12.28	Thyroxin 0·8 mg.	—	70–80	—	—	—	
4.1.29	1·6	—	80–90	40·0	3·3	0·24	
2.2.29	1·6	—	80–90	48·2	—	—	
8.2.29	1·6	—	80–90	62·2	4·7	0·12	
16.2.29	2·4	—	80–90	—	—	—	
25.2.29	2·4	—	80–90	70·8	4·1	0·14	
15.3 29	2·4	—	80–90	53·0	3·3	0·14	
25.4.29	2·4	—	80–90	63·5	5·8	0·14	
15.5.29	2·4 (Stopped)	−16 %	80–90	50·3	7·3	0·14	Oedema disappearing
1.7.29	0	—	—	151·4	—	—	

NOTE.—All alterations in dosage of thyroxin are recorded, the dose given being continued until the next change shown. The basal metabolic rate determinations are on the basis of the weight prior to the onset of the disease.

On Dec. 13 he had a large haematemesis. On Jan. 4, 1929 the haemoglobin was only 20 per cent., and on Jan. 7 he was given a transfusion of 650 c.c. whole blood. During this time treatment consisted in high protein and low fat diet, thyroxin by mouth, and salyrgan intravenously. He did well, the oedema disappearing, and the general condition improving, until April 24, 1929, when he had a large haemoptysis, and collapse of the L. lung. X-ray showed evidence of a tuberculous lesion, though the sputum was negative on seven occasions. Clinically there were signs of partial collapse of the L. lung, which gradually cleared up. His general condition became worse, however, and there was a tendency for oedema to return in the ankles. He commenced vomiting, and the blood non-protein nitrogen rose to 150 mg. per 100 c.c. His parents were anxious to have him at home, and were allowed to do so.

Records of thyroxin treatment, blood tests, &c., are given above.

Appendix II.   Details of Experiments.

The animals used were frog tadpoles (*Rana temporaria*), kept in vessels each containing the same amount of water (350 c.c.).   The water was changed daily, fresh additions of urine, thyroxin, &c. being made as recorded.   For food, cooked meat in ample quantity was given twice or thrice weekly.   Each group consisted of tadpoles of approximately the same size and stage of development.

Group A.   8 tadpoles.   From June 10 to 17, 12 c.c. of urine from R. W. was added to the water daily, with the exception of two days when water only was given.   On June 19, 10 c.c. urine was added, and on June 20, 5 c.c.   Up to that date the animals appeared normal.   On June 21, all but one of them were found dead.   From then until the conclusion of the experiment, water only was given.

Group B.   8 tadpoles.   These received normal urine in which thyroxin had been dissolved in the proportion of 0·4 mg. per 100 c.c.   From June 10 to 17, the amount was 12 c.c. daily, with the exception of two days, when the animals appeared ill.   By June 16, this group was definitely further advanced than either A or D, but two of the tadpoles had died.   On June 18 they were distinctly frog-like, with definite fore-limb buds.   4 more had died (see Plate 3, Fig. 2).   Though no more urine or thyroxin was administered, the remainder died on June 20.

Group C.   8 tadpoles.   0·2 mg. thyroxin only was added to the water daily except 14.6.29 and 16.6.29.   This group was obviously the most advanced as early as the fifth day of the experiment (14.6.29).   By June 17, some had definite fore-limbs, but all had died by June 18 (Plate 3, Fig. 3).

Group D.   8 tadpoles.   These received the same treatment as group A, but in this case with normal urine instead of that from the patient.   They appeared normal until June 19, when all were found dead.

Group E.   5 tadpoles.   Treatment was started on June 18, the animals being selected to be at the same stage of development as group A.   They were given normal urine in which had been dissolved only 0·07 mg. thyroxin per 100 c.c.   12 c.c. daily was administered for three days, after which water only was given.   By June 28 they were distinctly further advanced than group A (Plate 3, Fig. 4).

Group F (4 tadpoles) started on June 21, and received urine from patient W. G., to which had been added 0·3 mg. thyroxin per 100 c.c.   5 c.c. daily for 5 days was given, after which they received water only.   These also exceeded group A in rapidity of development (Plate 3, Fig. 4.).

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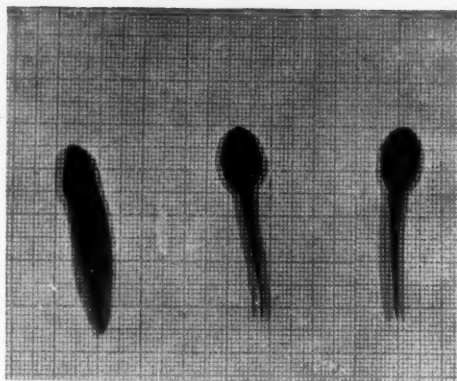
FIG. 1. Commencement of experiment, 11 June.
The paper underlying the tadpoles is
ruled in millimetres
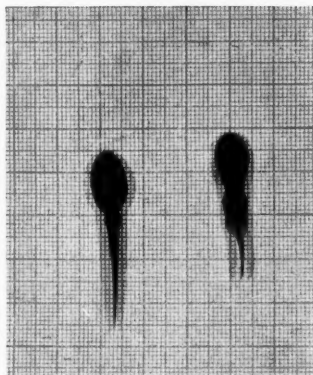
FIG. 2. A and B, 18 June.
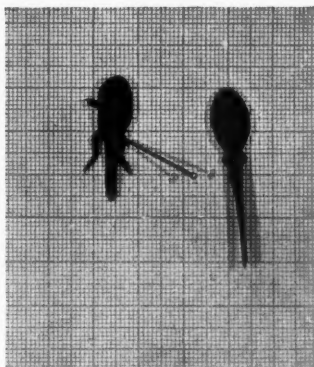
FIG. 3. C and D, 18 June.
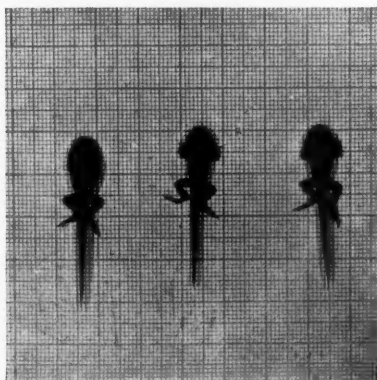
FIG. 4. A, E, and F, 28 June.

PARADOXICAL EMBOLISM [1]

By THEODORE THOMPSON and WILLIAM EVANS
(From the London Hospital)

With Plates 4 and 5

Embolism of the pulmonary artery or its branches is usually secondary to thrombosis established in the systemic veins or in the right chambers of the heart. Occasionally, tumour embolism results from the separation into the blood-stream of a portion of growth which has invaded and entered the systemic veins.

Emboli in the general systemic circulation are derived from thrombi in the left heart associated with disease of the mitral or aortic valves, and occasionally from thrombi formed in the aorta and large arteries, especially when these are the subject of aneurysm. In rare instances the embolus consists of an athero-matous fragment which has separated from the aortic valve, or from the wall of one of the large vessels. In rarer cases still, a portion of a primary growth of the myocardium situated in the left auricle or left ventricle has formed the embolus.

A small group remains where thrombosis in the systemic veins is associated with an embolus in the general systemic circulation. In these cases the embolus passes from the right to the left side of the heart through a patent foramen ovale, and the condition is then termed a crossed or paradoxical embolism.

The path of the embolus through an opening in the cardiac septum was first traced by Cohnheim (1) in 1876. He demonstrated a recent embolism of the right middle cerebral artery in a case of widely patent foramen ovale, with thrombosis in the veins of the lower extremities.

Five years later Zahn (2) was able to demonstrate, in a case of extensive thrombosis of the iliac veins, a long embolus, the thickness of a pencil, passing through a persistent foramen ovale. The head of the embolus was found projecting into the left auricle. A similar observation was made by Hauser (3) in 1888.

Rostan (4) analysed the records of 711 autopsies and found the foramen ovale occluded by a thrombus in three cases, whilst in seven cases he considered that the embolus found in the systemic circulation had passed through a patent foramen ovale. This condition he termed ' crossed embolism '. Van Reckling-hausen suggested the term ' paradoxical embolism '.

[1] Received July 8, 1929.

Ohm (5), in 1907, collected eleven cases of paradoxical embolism from the literature and reported a case of his own where thrombosis in the haemorrhoidal veins was complicated by two attacks of cerebral embolism. The patient had survived the first attack which had resulted in a left hemiplegia, but died three weeks later following a second attack. At necropsy the foramen ovale was found to be patent.

Versé (6), in 1909, described two cases. In one of these (a man, aged 70 years), an embolus (13 cm. long) derived from the iliac veins, lay astride a patent foramen ovale large enough to admit a lead pencil. Part of the embolus was found in the right auricle and part in the left auricle. Death had resulted from pulmonary embolism, and a crossed embolism of the right cerebral artery, followed by a left monoplegia, had occurred four days earlier.

Beattie (7), in 1925, reported two cases. In one, the paradoxical embolism was associated with pulmonary embolism; the patient had survived and appeared to improve a little following the onset of symptoms, which pointed to the occurrence of pulmonary embolism, but died two hours after the commencement of the attack. At necropsy a patent foramen ovale was found guarded by a long valvular fold. The significance of these findings will be discussed later.

Through the courtesy of Dr. T. R. Elliott, we have been able to study another case of paradoxical embolism. A female, aged 35 years, who had for eight months suffered from abdominal pain, came under observation following an attack of profuse haematemesis. On examination the spleen was found to be enlarged. Anaemia persisted after recovery from the haemorrhage, and the diagnosis of *Splenic Anaemia* was made. Splenectomy was performed without difficulty, but on the eighth day after operation the patient died suddenly, as from a pulmonary embolism. At necropsy, an embolus (eleven inches long and one-third of an inch in diameter) was found, held by its middle in the foramen ovale, with its free parts coiled on either side of the septum in the cavities of the right and left auricles. (See Pl. 4. Fig. 1.) The left internal iliac vein contained antemortem clot, and there was a septic infarct in the lower lobe of one lung. The intracardiac clot was regarded as the probable cause of sudden death.

Wittig (8) cited a case from the clinic of Muller, in which the diagnosis was made during life and confirmed at necropsy. The patient, a female aged 55 years, was found after exploratory laparotomy to have carcinoma involving both ovaries. On the twelfth day after operation the patient became suddenly very distressed, and the diagnosis of pulmonary embolism was made; she improved, and the cyanosis disappeared. An hour or so later the patient experienced pain and weakness of the right arm, and the right radial pulse was found to be absent. This was followed, twelve hours later, by weakness of the left leg and severe pain behind the right ear. A diagnosis of paradoxical embolism of right subclavian and common carotid arteries was made, and the patient died two hours later. Autopsy revealed thrombosis in the left deep femoral vein, left ovarian vein, and left vesical plexus; recent emboli in both branches of pulmonary artery; a long embolus lying in a patent foramen ovale,

part of it presenting in the right auricle and part in the left; paradoxical emboli in the innominate, right subclavian, and right common carotid arteries; recent softening of the right cerebral hemisphere; old scarred infarcts in both kidneys.

Our attention has been drawn to another instance of paradoxical embolism which occurred recently in the practice of Mr. Ferguson Young at the Sheffield Royal Hospital. A distended inflamed gall-bladder, caused by the presence of an impacted calculus, was removed at operation in a female patient aged 70 years. The patient made satisfactory progress until the third day following the operation, when she suddenly became very breathless and died within five minutes. Necropsy revealed an embolus as thick as an ordinary pencil and about $2\frac{1}{2}$ inches long, coiled on itself in the pulmonary artery at the point of its bifurcation into the right and left branches. Within the heart a second embolus of about the same length and thickness was found, passing through the foramen ovale from the right auricle into the left. Its complete passage had been prevented by the presence of a bifurcation. The short truncated branches, which passed off at practically right angles to the main stem, were placed opposite to each other, and were sufficiently widely spread to overlap the margin of the foramen. The embolus was continued through the left auricle and the mitral valve to reach the apex of the left ventricle, where its tapered terminal portion was found to be doubled on itself. The embolus is well seen in the accompanying photograph. (Pl. 5, Fig. 2.) The site of origin of the emboli could not be ascertained. There was no evidence of thrombosis in the inferior vena cava, common iliac, external iliac, internal iliac, ovarian, or subclavian veins, whilst the vessels of the operation area appeared healthy.

Recently we have been able to collect five cases of paradoxical embolism. In addition to placing these cases on record, we propose in this paper to present and analyse certain interesting problems arising from their study.

Types of Paradoxical Embolism.

Both clinically and pathologically there appear to be three distinct types of paradoxical embolism. In all three groups the embolus has travelled from the right heart to the left heart through a persistent foramen ovale or patent interventricular septum, but the subdivision is made possible, and becomes necessary, when the nature or the character of the embolus is considered; thus it may consist of a simple thrombus, a fragment of new growth, or a piece of septic material.

(a) *Thrombosis as a cause of the embolism.* It will be seen from the review of the literature that in most of the reported cases of paradoxical embolism, thrombosis in the venous circulation had supplied the source of the embolus. Four of our five cases fall in this group. In each of these the thrombosis had formed in the femoral veins. In two cases pulmonary embolism was also present, and the significance of the relationship between pulmonary and paradoxical embolism will be discussed later. *Case 1* is interesting in that the

diagnosis was made during life, and is unique in that the patient recovered not only from pulmonary embolism, but also from a cerebral embolism of the paradoxical type.

Case 1. Female, aged 38 years. On August 24, 1928, an appendix distended with mucus was removed by operation. There was no recent acute inflammation. On September 8, the patient developed painful oedema of her right leg. On September 11, she complained of severe pain in the right chest in the posterior axillary region; the pain was accentuated on coughing and deep inspiration, and accompanied by the expectoration of a little dark blood. The temperature, which had previously remained normal, rose to 101° F.
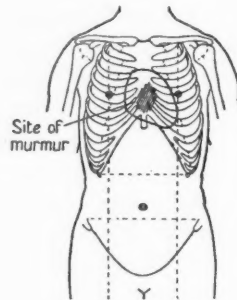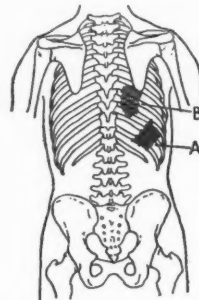
FIG. 3.   FIG. 4.

On examination by one of us (Th. Th.), impairment of percussion note was elicited over an area indicated in the diagram at A (Fig. 4). A pulmonary infarct was diagnosed. On September 16, at 10.30 p.m., the patient again complained of severe pleuritic pain in the right side, and the percussion note was found impaired over an area as shown at B (Fig. 4). The diagnosis of pulmonary infarction was again made. Two and a half hours later, at 1 a.m., the patient developed complete motor aphasia, with right hemiparesis. Cerebral embolism of the paradoxical type was diagnosed. The hemiparesis disappeared in three weeks, but motor aphasia remained complete for six weeks, and some hesitation and difficulty in finding correct words still persisted when last examined on March 28, 1929. A slight soft systolic murmur over the lower part of the sternum was not conducted to the axilla, and there was no evidence of cardiac enlargement.

The patient returned to her work as secretary to a medical man, and has done her work satisfactorily in spite of the fact that she had to relearn her alphabet and the use of the typewriter. The fact that a complete recovery was made in this unique case is clear evidence that the case could not have been one of ulcerative endocarditis of both right and left sides of the heart, with emboli in both pulmonary and systemic circulations. The systolic murmur heard over the base of the heart was evident before the operation, and was considered to be a slight congenital defect of the interventricular septum or a patent foramen ovale. The occurrence of a pulmonary embolism shortly preceding the crossed cerebral embolism is noteworthy in this case.

Case 2. Male, aged 61 years, was admitted to hospital for the removal of a 'loose body' from the right knee joint. Recovery had been uninterrupted until the fifteenth day after operation, when the patient complained of sudden and severe pain in the chest which was accompanied by extreme dyspnoea and,

later, some blood-stained sputum. Pulmonary embolism was diagnosed, but the patient survived for forty-eight hours, and then died suddenly.

Findings at necropsy. Externally laminated thrombus (1 cm. diam.) coiled up in right main pulmonary artery and completely blocking it, with a branch (0·6 cm. diam.) riding the bifurcation and lying in left pulmonary artery. Numerous haemorrhagic infarcts, occupying greater part of right lower lobe, with slight fibrinous pleurisy over them, and collapse of the intervening portion of the right lower lobe. Haemorrhagic infarct (2 cm. diam.) in lower and posterior border of left lung. Agonal thrombus and portions of externally laminated ante-mortem thrombus in both femoral veins and their tributaries. Foramen ovale widely open (0·8 cm. diam.) and protected by a valve. No thrombus or other abnormality in heart. Paradoxical embolus riding bifurcation of left main renal artery. Mottled pink and dull red infarction, with slight swelling of whole of left kidney. One completely necrosed anaemic infarct with haemorrhagic border (1 cm. diam.) in left kidney, and another (1 × 0·5 cm.) in otherwise normal right kidney. Wedge-shaped area of slightly haemorrhagic softening (infarct) (1·3 × 1 × 0·8 cm.) in cortex of left upper anterior occipital region of brain. (See Pl. 2, Fig. 5.)

Case 3. Male, aged 34. Five weeks previously, rib resection had been practised for the drainage of an empyema which had followed lobar pneumonia affecting the right lower lobe. The wound had continued to discharge, but the patient's general condition had gradually improved until four days before admission to hospital ; he had then complained of severe headache accompanied by vomiting ; later he became drowsy and aphasic.

On examination he was found to be in a semi-comatose condition, and when roused presented complete motor aphasia. A right hemiplegia was present. The optic disks appeared normal. There was well-marked oedema of the right foot and leg, but no palpable thrombosis of the femoral nor popliteal veins. The diagnosis of paradoxical embolism was suggested, but later the skull was trephined and the brain needled for a cerebral abscess, with negative results. The patient died two days after the operation.

Findings at necropsy. Drainage opening through absent portion of tenth right rib at its angle. Collapsed right lower lobe, with numerous small areas of pink granular pneumonic consolidation. No thrombosis of pulmonary veins nor arteries. Patent foramen ovale (0·6 cm. diam.), protected by a valvular fold. No thrombus in cardiac chambers and no evidence of endocarditis. Pale granular thrombus in main branch of splenic artery in centre of hilum of spleen. Large subacute septic spleen, with recent, partly anaemic, partly haemorrhagic infarct (10 cm. from side to side × 5·5 × 4 cm.) crossing the whole spleen just above its middle. Slightly smaller infarct in upper pole of spleen, and one (2·8 cm. diam.) in posterior border. Pink and grey ante-mortem thrombus fixed in bifurcation of one of the two main branches of the left middle cerebral arteries 1·8 cm. from origin of middle cerebral artery. No signs of infarction found in brain. Slight oedema of both ankles. Lightly adherent pink and red thrombus filling both femoral veins.

Case 4. Female, aged 30 years. Delivered of a child seven weeks previously. One week before admission to hospital had a shivering attack, followed by drowsiness and, later, weakness of the right arm and leg.

Examination revealed a right hemiplegia. There was evidence of pulmonary tuberculosis, and tubercle bacilli were discovered in the sputum. There was oedema of both feet. The heart was clear. A remittent pyrexia was present throughout the illness, and the patient died four weeks after admission.

Findings at necropsy. Adherent thrombus in left vesical, and vaginal veins, in left internal, common, and external iliac veins, in left common and superficial femoral veins, in left popliteal vein, and in venae comites of the left

posterior tibial artery. Adherent granular thrombus in right uterine veins. Placental relics on anterior wall of involuted uterus. Foramen ovale patent (0·3 cm. diam.), and guarded by a valvular fold. Dilatation of right ventricle. Lungs showed changes due to tuberculosis ; there was no pulmonary embolism, and no thrombosis in the pulmonary vein or its tributaries. Area of anaemic softening (1·5 × 0·7 cm.) in white matter, 0·5 cm. below the cortex of the inferior genu of the left ascending frontal convolution of brain. Middle ears clean. Multiple recent anaemic infarcts in both kidneys. Microscopical examination revealed thrombotic embolus in arcuate artery of kidney. Anaemic scarred infarct in enlarged congested septic spleen.

TABLE I. *Illustrating the main features presented by the five cases recorded in this paper.*

Case No.	Age.	Sex.	Source of Embolus.	State of Foramen Ovale.	Site of Para-doxical Embolism.	Pulmonary Condition.
1	38	F.	Thrombosis of right femoral vein	Patient survived. (Systolic murmur over sternum)	Cerebral	Pulmonary infarction
2	61	M.	Thrombosis of both femoral veins	Patent to pencil	Renal Cerebral	Pulmonary embolism
3	34	M.	Thrombosis of both femoral veins	,, ,, ,,	Splenic Cerebral	No evidence of pulmonary infarction
4	30	F.	Thrombosis of left iliac and femoral veins	Patent to probe	Cerebral Renal	,, ,, ,,
5	25	M.	Malignant teratoma of testes	,, ,, ,,	Cerebral Coronary	No evidence of growth

(*b*) *Tumour embolus.* Metastases of tumour masses through a patent foramen ovale were first demonstrated by Zahn (9) in 1889. Our investigation of tumour embolism of the paradoxical type has established this complication to be a very rare occurrence, and great care and caution must be exercised, even at necropsy, to exclude the possibility of the embolus having traversed the lesser or pulmonary circulation in its path from the venous to the general arterial circulation. In order to investigate this problem more fully, a study was made of fifteen cases where a secondary neoplasm of the brain was found at necropsy. In each case the secondary deposits had resulted from haematogenous spread. The main and essential features of these cases are best set out in a table. See Table II.)

In eight of the fifteen cases the primary growth was located in the lungs, and was found to arise in connexion with a bronchus. In some of these, carcinomatous invasion of the walls of the larger radicles of the pulmonary veins was evident with the naked eye, and occasionally protrusion of the growth on to the intimal surface of the veins could be seen. In the remaining seven cases the primary growth had occurred at some site other than in the lungs, but here with one exception secondary deposits were present in the lungs as well as the brain. In Case No. 4 in the table there was no evidence of growth in the lungs on macroscopical examination, but microscopical examination was not conducted.

It is clear, however, that in the absence of an open foramen ovale the neoplastic cells must have traversed the pulmonary circulation in this case in their path from the colon to the brain. In three cases the foramen ovale had remained patent, but in each of these extensive secondary deposits were present in the lungs, and therefore it would be a fallacy to assume that the growth had passed through the open foramen.

TABLE II. *Giving further details of the fifteen cases where secondary neoplasm of the brain had resulted from haematogenous spread.*

Case No.	Character of the Primary Growth.	Presence or absence of Growth in the Lungs.	State of the Foramen Ovale.	Site of the Secondary Growth Deposit in the Brain.
1	Carcinoma of bronchus	Present	?	Centrum semiovale
2	,, ,, uterus	,,	Closed	,,
3	,, ,, bronchus	,,	Patent to probe	Cerebellum
4	,, ,, colon	Absent	Closed	Temporo-sphenoidal lobe
5	,, ,, bronchus	Present	,,	Cerebellum
6	Ectopic chorion epithelioma	,,	,,	,,
7	Carcinoma of rectum	,,	,,	Centrum semiovale
8	,, ,, bronchus	,,	Patent to pencil	Cerebellum and optic thalamus
9	,, ,, ,,	,,	Closed	Frontal lobe
10	,, ,, ,,	,,	,,	Cerebellum and caudate nucleus
11	,, ,, ,,	,,	,,	Parietal lobe
12	Chorion epithelioma	,,	Patent to pencil	Cerebral cortex
13	Carcinoma of bronchus	,,	Closed	Cerebellum
14	,, ,, uterus	,,	,,	,,
15	Osteo-sarcoma of knee	,,	,,	Occipital lobe

We are, however, able to record one authentic case of tumour embolus of the paradoxical type.

Case 5. Male, aged 25 years. Five days before admission to hospital, fell when at work in a signal box. He remained unconscious for seven minutes and never properly rallied.

On examination the patient appeared listless, but when roused he answered questions intelligently. The cranial nerves appeared normal. A left hemiplegia was present. The breathing, which at first was slow and quiet, suddenly became noisy and stertorous, the pulse-rate became rapid, coma supervened, and the patient died within half an hour of admission to hospital.

Findings at necropsy. Malignant teratoma involving both testes. Foramen ovale patent to probe. Mass of growth, the size of a cherry, attached to the right surface of the interauricular septum, a portion of this was found to project through the patent foramen ovale into the left auricle. Large polypoid mass of growth projecting from the wall of the left ventricle, a similar mass of growth lying free within the cavity of the left ventricle. Growth embolus in both coronary arteries. Growth embolus blocking the right middle cerebral artery at the point of its first bifurcation. Anaemic softening of the right temporal lobe, the posterior two-thirds of the outer surface of the parietal lobe (with the exception of the superior parietal convolution), and the right island of Reil extending to, and including the putamen of the lenticular nucleus. Congestion and no evidence of growth in lungs. The growth in coronary and right middle cerebral arteries on microscopical examination proved to be similar in nature to the primary growth in the testes.

Case 12 in Table II was at one time regarded to be another example of paradoxical growth embolism, but a more careful study of the case proved its inclusion in this group to be unjustifiable. In this instance the foramen ovale was patent (0·6 cm. diameter) and protected by a valvular fold. Secondary deposits from a chorion epithelioma of the uterus were present in both lungs, cortex of the cerebrum, spleen, and mucosa of the small intestines. A portion of growth, (1 cm. long) was found to fill the left middle cerebral artery, and there was similar obstruction of its main branch for 3 cm. from its origin ; red thrombus was found in the distal portion of the artery, and there was some evidence of softening of the left parietal lobe.

The presence of secondary deposits in the lungs, deposits in the cerebral cortex, the existence of a valve guarding the patent foramen ovale, the absence in the clinical history of a sudden onset of hemiplegia, and the fact that the growth in the cerebral artery was found to be intimately connected with the vessel wall for a distance of 4 cm., are all factors that preclude the inclusion of the case in this group.

Before passing on to discuss the other type of paradoxical embolism, we would like here to formulate certain guiding rules that should lead to the more accurate diagnosis of the exact nature of growth or tumour embolism :

(1) If growth is present in the lung, great caution must be exercised, even in the presence of a patent foramen ovale, to exclude the possibility of the tumour embolus having traversed the lesser or pulmonary circulation.

(2) Secondary growth deposits in the lung should be excluded by microscopical examination.

(3) The suspected growth embolus should lie free within the lumen of the artery. If it is intimately associated with the vessel wall as in Case 12, its formation has probably resulted from the gradual proliferation of neoplastic cells previously deposited on the intima of the vessel, and such a finding favours the view that the neoplastic cells have arrived there through the pulmonary vessels.

(4) When the growth is found in the middle cerebral artery, the presence of other deposits in the cerebral cortex suggests that the neoplastic cells have traversed the pulmonary circulation.

(5) When tumour embolus of the paradoxical type has its situation in the cerebral vessels, then the clinical notes should provide a history of the sudden onset of some grave symptom such as a hemiplegia with or without loss of consciousness.

(6) When a patent foramen ovale is protected by a valvular fold, then the tumour embolism of the paradoxical type can only result following the primary infiltration of the growth along the interauricular wall in the right auricle, and finally its direct extension through the foramen.

(c) *Infective or septic embolus.* In 1904 Buhlig (10) reported a case of generally disseminated tuberculosis; he described the case at great length and contended that the primary seat of tuberculosis in this instance was confined to

the abdomen, that the pulmonary lesions had been established secondarily to the abdominal condition, and that the miliary granulomatous tubercles found in the various organs had formed as the result of the dissemination of tubercle bacilli through the avenue of an open foramen ovale. His conclusions, however, are not convincing, and for the most part are hypothetical. Abbott, Lewis, and Beattie (11) stated that 'cerebral complications of the nature of abscess or infarction are a frequent complication of congenital cardiac cases presenting defects in the interauricular or interventricular septum, and are in the great majority of cases embolic in nature from a focus in the venous system (paradoxical or crossed embolism)'. We note that in many of the cases which they reviewed, and on which they apparently based their conclusions, no detailed account of the findings at autopsy were given.

In this group it is even a more hazardous task to predict with any degree of certainty the exact path taken by bacteria or minute fragments of infective material from some part of the venous circulation to a focus in the arterial system. In 22 out of 195 cases of brain abscess investigated, the abscess was found to have been established in a general systemic pyaemia, where the infected material had been transmitted to the brain-stem by the blood-stream from various foci drained by the venous system. In 12 of these cases where the foramen ovale was found to be closed, the infected material must have traversed the pulmonary circulation ; in 8 of the 12 cases pyaemic abscesses were found in the lungs, whilst in the remaining 4, lung abscesses had not been discovered on macroscopical examination. In 7 cases the foramen had remained patent, and 5 of these demonstrated pyaemic lung abscesses. A more detailed analysis of these figures will be found in Table III.

TABLE III. *Giving further details of twenty-two cases where brain abscess had resulted from a general systemic pyaemia.*

State of Foramen ovale.	Total Cases.	Pyaemic Abscesses in Lungs.	Lung Abscess not discovered.
Closed	12	8	4
Patent to probe	4	2	2
Patent to pencil	3	3	—
Not noted	3	1	2

From a study of these cases the difficulty of tracing the path of infection in any particular case will be readily appreciated, for the facility with which infection passes through the pulmonary circulation renders it doubtful even in the presence of a patent foramen ovale, unprotected by a valve, whether this route affords in any single instance the common path traversed by bacteria in their transit from the general venous to the arterial system.

Site of the Embolism.

One of the cerebral arteries, and usually the middle cerebral artery or one of its branches, appears to provide the seat for the embolism in the majority of

cases. Cerebral embolism was present in each of our 5 cases, in 4 of them it occurred on the left side, and on the right side in the remaining case. Para- doxical embolism is, however, seldom confined to the cerebral arteries, and usually the lesion is multiple. In our cases it occurred in the cerebral and renal arteries in 2 instances, in the cerebral and splenic arteries in 1, in the cerebral and coronary arteries in 1, while the cerebral artery alone appeared to be involved in a case which survived the embolism. Wittig (8), in his review of a series of cases, found that the renal arteries were involved in 44·5 per cent., and that in over one-third of these both kidneys were affected. In a series of 13,234 consecutive necropsies we found cerebral embolism present in 49 in- stances. The source of the embolism in each case is indicated in Table IV. The embolism proved to be of the paradoxical variety in 2 cases. This con- dition, therefore, appears to have an incidence of a little over 4 per cent. of all cases of cerebral embolism. Occasionally the arteries of the neck and those to the upper and lower limbs have provided the seat for the embolism.

TABLE IV.   *Illustrating the source of the embolus in forty-nine cases where cerebral embolism was discovered at autopsy.*

Source of the Embolus.	Number of Cases.
Ulcerative and infective endocarditis	28
Mitral stenosis (Ante-mortem clot in L. auricle)	9
Atheromatous ulceration of aorta	3
Agonal embolism	3
Thrombosis in an aortic aneurysm	2
Tumour embolism (Primary sarcoma of L. ventricle)	1
Idiopathic thrombosis in L. ventricle	1
Paradoxical embolism	2

Incidence and Degree of Patency of the Foramen Ovale.

Many anomalies are produced by the persistence during adult life of some vestigial structure peculiar to the foetal circulation. The commonest of these foetal relics is a patent foramen ovale.

From the combined statistics of Bizot, Ogle, Klob, Wallman, Rostan, and Hinze (12), we learn that in 2,087 hearts examined the foramen was found patent in 632 or 30 per cent. Fawcett and Blachford (13), investigating the frequency of an opening between the right and left auricles, found the foramen ovale to be patent in 31 per cent. of cases examined; all their cases, however, were subjects over 10 years of age.

TABLE V.   *Showing the incidence and degree of patency of the foramen ovale in 1,100 consecutive cases examined at necropsy.*

State of the Foramen Ovale.	Diameter of Patent Foramen.	No. of Cases.	Incidence.
Closed	—	714	65 %
Patent to probe	0·2 cm.	319	29 % } 35 %
Patent to pencil	0·7 cm.	67	6 %

In order to ascertain the incidence of patent foramen ovale we examined the records of 1,100 consecutive necropsies and found the foramen to be patent in 35 per cent. The degree of patency had been tested by insertion of a probe or pencil, and accordingly the patency of the foramen was recorded as F.O.P.Pr (foramen ovale patent to probe or 0·2 cm. diameter) or F.O.P.Pl (foramen ovale patent to pencil and equivalent to 0·7 cm. diameter). In this series the foramen was found to be closed in 714 or 65 per cent., patent to probe in 319 or 29 per cent., and patent to pencil in 67 or 6 per cent. of the cases. (See Table IV.)

Where the foramen had remained patent to probe, 89 of the 319 cases were infants under six months old; the average age of the remaining 230 cases was 20 years, whilst 36 of these were subjects of 50 years of age or older.

In the third group, where the foramen had remained widely open, 34 were infants under 6 months old, but the average age of the remaining 33 cases was as high as 30 years, whilst 9 of these were subjects of 50 years of age or older. In a great many of these cases the foramen was guarded by a valvular fold. In young infants the non-closure of the foramen was also associated with the persistence of some other vestige of the foetal circulation such as patency of the ductus arteriosus and ductus venosus.

The Relationship between Paradoxical and Pulmonary Embolism.

In 50 per cent. of Wittig's (8) cases, paradoxical embolism was found to be associated with pulmonary embolism. In 24 per cent. pulmonary embolism had preceded the paradoxical embolism, and in these cases obstruction within the lesser or pulmonary circulation was considered to be the main cause in its establishment.

In our Cases 1 and 2, pulmonary embolism had preceded embolism of the paradoxical type. In Case 3 there appeared to have been no preliminary embarrassment of the pulmonary circulation. In Case 4 necropsy revealed chronic pulmonary tuberculosis with dilatation of the right ventricle, but there was no evidence of pulmonary embolism.

Pulmonary embolism was regarded by Beattie (7) to have given rise to the further complication of paradoxical embolism in one of his two cases. In Wilson's case (recorded in this paper), pulmonary embolism was regarded to have played a similar role in the etiology of an embolus of the paradoxical type.

A study of the intra-auricular blood-pressure appears to establish the pressure to be higher in the left auricle than in the right. Under these circumstances a patent foramen ovale protected by a valve remains competent, the higher pressure in the left auricle tending to keep the valve closed; in this way an opening which remains patent anatomically becomes competent physiologically. Anything which tends to disturb this pressure relationship by raising the pressure within the right auricle and reducing the pressure in the left auricle would produce incompetency of the valve and allow the blood to flow

from the right to the left auricle and in this way re-establish in part the foetal circulation.

Haggart and Walker (14) conducted an investigation on these lines, and attempted to record the effect of graded pulmonary arterial occlusion upon the systemic and pulmonary blood-pressure. In a series of experiments on cats they produced a partial or complete block of the pulmonary artery—a condition analogous to pulmonary embolism in man. They found that sudden occlusion of the left branch of the pulmonary artery caused an immediate rise in the pulmonary pressure averaging about 29 per cent., whilst following total pulmonary occlusion the pulmonary pressure increased rapidly by 121 to 267 per cent. At the same time there was an immediate fall of the systemic arterial blood-pressure.

This experimental evidence is supported and illustrated clinically by our Cases 1 and 2. In both instances the paradoxical embolism supervened some time after the onset of pulmonary embolism. Although the latter had proved inadequate to cause instant death of the patient, nevertheless it had produced a sufficient degree of depletion of the pulmonary circulation to effect a considerable rise of pressure within the right heart, and consequently favoured the transmission through the patent foramen ovale of any further embolus arriving in the right auricle from the source of the venous thrombosis.

Case 2 also illustrates how a patient may survive lung embolism, develop a paradoxical embolism, and then develop further pulmonary embolism, which proves fatal.

In order to investigate this question more fully, we analysed the clinical and post-mortem records of 112 consecutive cases of pulmonary embolism. In 88 of these the foramen ovale was found to be closed. In the remaining 24 cases, although the foramen had remained open, paradoxical embolism had not occurred as an added complication. To facilitate the study of this group, we have tabulated the main details of the cases in Table VI.

In 18 instances pulmonary embolism had supplied the cause of death, but in Cases 3, 4, 5, 12, and 18, peritonitis, perforated typhoid ulcer, pyaemia, bronchopneumonia, pericarditis and broncho-pneumonia, respectively, had provided the cause of death. In each of these it will be noted that only one-fourth or less of the pulmonary circulation had been rendered inactive by the embolism. Case No. 17 is instructive and demands further mention. The patient, while convalescent from her operation, developed shortness of breath of sudden onset. She was seen by Dr. John Parkinson, who diagnosed pulmonary infarction resulting from embolism. The patient gradually improved until three weeks later, when she suddenly died following another severe attack of breathlessness. At autopsy the right ventricle was found to be dilated and showed some degree of hypertrophy. These findings appear to indicate that a condition of increased pressure in the pulmonary circulation had existed since the initial onset of pulmonary infarction three weeks previously, and yet in the presence of a patent foramen ovale, embolism of the paradoxical type had not occurred.

TABLE VI. *Presenting a more detailed analysis of the twenty-four cases where pulmonary embolism was found at necropsy to be associated with a patent foramen ovale.*

Case No.	Age	Sex	Primary Conditions which lead to Thrombosis.	Site of the Venous Thrombosis.	Extent to which Pulmonary Ventilation was Depleted.	State of Foramen Ovale.	Manner of Death.
1	83	F.	Fractured femur	Femoral	$\frac{3}{4}$	Patent to probe	Sudden
2	10/52	F.	Gastro-enteritis	Renal	Complete	,,	,,
3	59	M.	Prostatectomy	Not discovered	1/5	,,	Gradual
4	33	M.	Typhoid	Common iliac	$\frac{1}{4}$	,,	Sudden
5	37	F.	Puerperal pyaemia	Saphenous	1/10	,,	Gradual
6	49	M.	Resection of Meckel's diverticulum	Not discovered		,,	Sudden
7	38	F.	Salpingectomy	,,		pencil	,,
8	23	F.	Partial gastrectomy	Uterine and common iliac	Complete	,,	,,
9	47	M.	Appendicectomy	Internal iliac	$\frac{1}{2}$	probe	,,
10	33	F.	Ovariotomy	,,	Complete	pencil	,,
11	46	M.	Encephalitis lethargica	External and internal iliac		probe	Gradual
12	52	M.	Gastro-jejunostomy	Not discovered	$\frac{1}{4}$	,,	Sudden
13	50	F.	Sub-total hysterectomy	Ovarian	Complete	pencil	,,
14	36	F.	Empyema—rib resection	Internal and external jugular	1/5	probe	No record
15	29	F.	Laparotomy	External iliac	$\frac{1}{2}$	pencil	Gradual
16	3/52	M.	Umbilical sepsis	Umbilical		probe	Sudden
17	50	F.	Cholecystectomy	Not discovered	Complete	,,	Sudden
18	19	F.	Salpingectomy	Internal iliac	1/5	pencil	Gradual
19	61	M.	Aortitis	Common iliac	Complete	probe	Sudden
20	65	F.	Colostomy	Femoral		pencil	,,
21	52	M.	Excision of rectal polyp.	Common iliac	,,	,,	,,
22	61	M.	Laparotomy	Not discovered	4/5 (ult.)	,,	Gradual
23	69	M.	Prostatectomy	,,	Complete	probe	Sudden
24	65	M.	Cerebral haemorrhage	"Femoral"	,,	pencil	,,

The opening, however, in this instance was small (0·3 cm. diameter). Case No. 22 illustrates the same phenomenon but to a lesser degree; here the patient had survived the first attack of pulmonary infarction, but died two hours and forty minutes later from further pulmonary embolism. The foramen ovale in this case remained widely open, but paradoxical embolism had not resulted.

From a consideration of all these data, therefore, it becomes clear that although in about one-half of the cases of paradoxical embolism, increase of pressure in the right auricle produced by non-fatal pulmonary embolism appears to provide an important factor in its etiology, yet in the remaining cases there appear no constant factors which govern or determine its establishment.

Based on this investigation we would summarize the most important factors involved in the formation of paradoxical embolism in its relationship to pulmonary embolism, as follows:

(1) To favour the establishment of paradoxical embolism by increasing the pressure in the right auricle it is essential that over one-third of the pulmonary circulation should be depleted by the pulmonary embolism. Moreover, should 50 per cent. or more of the pulmonary circulation be cut off suddenly by an embolus, death results within 10 to 30 minutes. Of 16 cases where the pulmonary circulation had been depleted to this extent, only one had survived a period of 30 minutes.

(2) When pulmonary infarction has resulted, and this has been large enough to raise appreciably the pulmonary pressure, and yet not be sufficiently extensive to produce sudden death it then becomes necessary for the production of a paradoxical embolus, that a further embolus should arrive in the right auricle from the venous system.

(3) Should this embolus represent a cast of the lumen of the larger systemic veins, as is often the case, and the foramen ovale remains patent only to a probe, then such an embolus again passes on to the pulmonary artery. Clearly, therefore, the relation between the size of the embolus and the degree of the patency of the foramen are additional and important factors in determining the production of paradoxical embolism.

When all these facts are reviewed it is not difficult to appreciate why paradoxical embolism should be a rare condition.

Diagnosis.

The diagnosis of the condition during life must remain a matter of speculation. If a patient, the subject of venous thrombosis, develops cerebral embolism, or in rare instances embolism involving an artery to one of the limbs, and if in such a patient there is no clinical evidence of any other cardio-vascular disease present, then it may be justifiable to assume that the embolism is of the paradoxical type. Should the embolism be preceded by the occurrence of pulmonary infarction, then the diagnosis becomes more certain.

At necropsy, also, great care must be exercised, even in the presence of venous

thrombosis associated with a patent foramen ovale, to exclude all other causes of arterial embolism discussed in the earlier part of this paper.

Summary.

The condition known as *crossed* or *paradoxical embolism* is defined. A review is made of the cases recorded in the literature. An account is given of an unpublished case from Sheffield. Three types of paradoxical embolism are described, and five authentic cases recorded in detail. The rarity of tumour and septic emboli of the paradoxical type is emphasized. Reference is made to the site of the embolism, and the incidence and degree of patency of the foramen ovale are discussed. Finally, the relationship between paradoxical embolism and pulmonary embolism is considered in detail, and mention is made of the difficulty experienced in the accurate diagnosis of the condition during life.

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DESCRIPTION OF PLATES.

FIG. 1. Showing the heart in Dr. T. R. Elliott's case. Both auricles have been laid open, and are viewed from above. The embolus which is coiled up in both auricles is seen passing through a widely patent foramen ovale.

FIG. 2. Showing the heart in Mr. Ferguson Wilson's case. The auricles and left ventricle are viewed from behind. The embolus extends from the right auricle to the apex of the left ventricle and is seen passing through a patent foramen ovale into the left auricle and finally through the mitral valve into the left ventricle.

FIG. 5. Showing a wedge-shaped haemorrhagic infarct in the cortex of the left upper and anterior portion of the occipital lobe of the brain in Case 2.
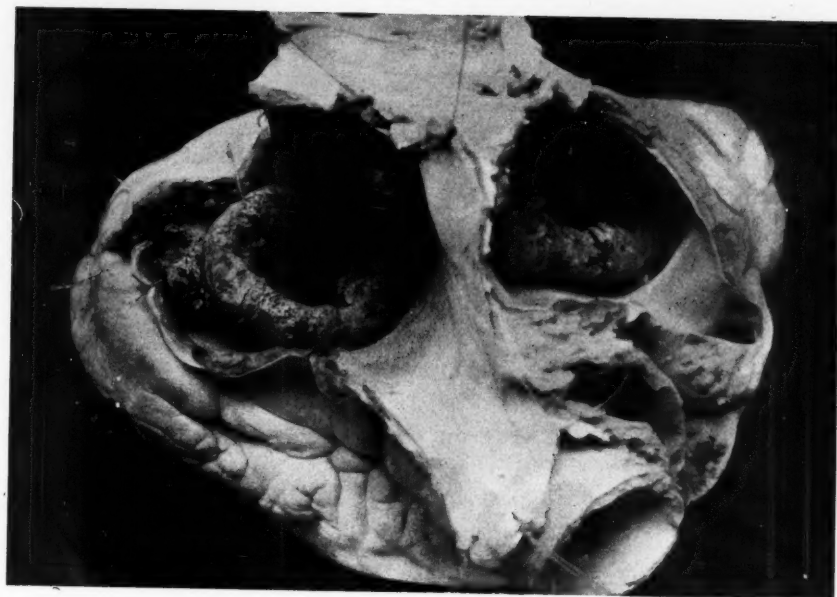
Fig. 1
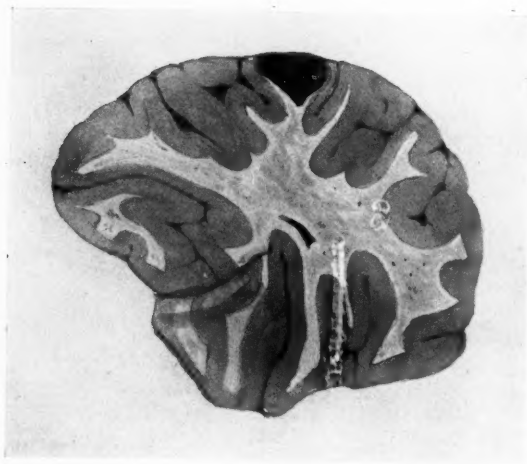
Fig. 5
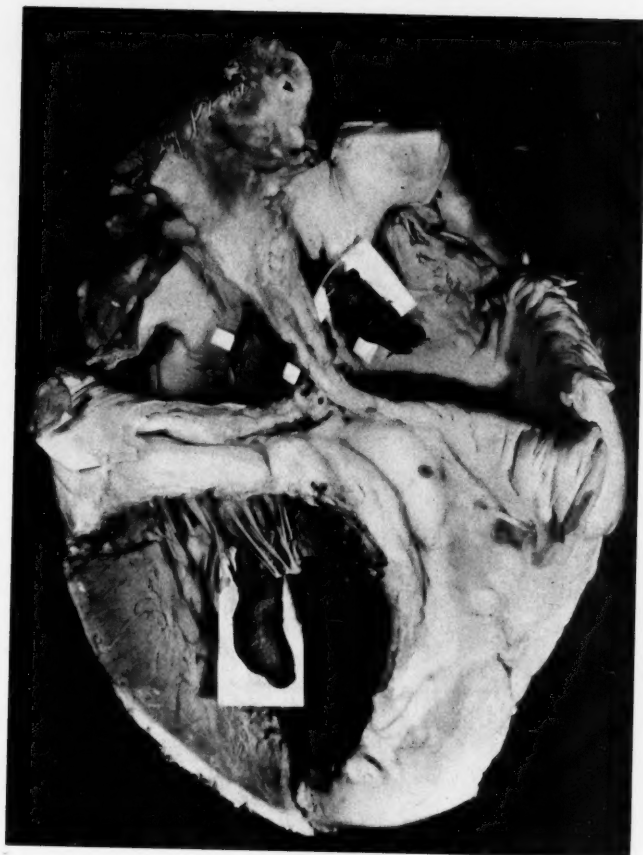
FIG. 2

PERIOSTEAL NEUROFIBROMATOSIS, WITH A SHORT CONSIDERATION OF THE WHOLE SUBJECT OF NEUROFIBROMATOSIS [1]

By F. PARKES WEBER

With the Collaboration of J. R. Perdrau

With Plates 6 to 9

NEUROFIBROMATOSIS is often called ' Recklinghausen's disease' from von Recklinghausen's description of multiple cutaneous fibromata in 1882 (1), but this is rather confusing, since the diffuse and generalized forms of osteitis fibrosa or fibrocystic disease of bones are also spoken of as Recklinghausen's disease, and in certain cases of neurofibromatosis there are bony thickenings which, when they are localized on the face or skull, may clinically be supposed to be due to osteitis fibrosa, one cause of the clinical appearances known as ' leontiasis ossea '. I believe, however, that the irregular cranial hyperostoses in cases of neurofibromatosis are probably due, not to the changes of osteitis fibrosa, but to neurofibromatous involvement of the periosteum, just as the irregular thickening of the shaft of the left tibia in the case we shall describe was secondary to the irregular localized neurofibromatosis of the periosteum. Hyperplasia of the bone underlying or close to a plexiform neuroma or a neurofibromatous ' pachydermatocele', 'neurofibromatous elephantiasis', and molluscous pendulous tumours, one form of so-called dermatolysis, has long been recognized as of occasional occurrence, and this doubtless applies to some of the cases of bony hyperplasia in the face and head in cases of neurofibromatosis.

Neurofibromatosis is evidently of congenital and developmental origin and is not rarely familial. In regard to the post-natal development of most of its worst manifestations it resembles many other developmental diseases that may be familial, such as generalized haemangiectasia of the skin and mucous membranes (hereditary epistaxis, &c.), multiple osteomata or exostoses, the delayed examples of hereditary oedema of limbs (the Milroy-Nonne disease, trophoedema, Meige's disease), progressive lenticular degeneration with hepatic cirrhosis or Wilson's disease, familial developmental ataxia, myotonia atrophica, hereditary cataract, and various primary muscular dystrophies.

As neurofibromatosis is the manifestation of a congenital developmental abnormality, it is not surprising that it should be occasionally associated with congenital malformations (2), such as spina bifida (3) and cerebral meningocele (4) (Pl. 6, Figs. 1 and 2), but perhaps this developmental connexion is aetiologically

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[1] Received July 13, 1929.

closer with unilateral buphthalmus (congenital glaucoma), and haemangiectatic and so-called 'anaemic' naevi (5).

The disease consists chiefly in the formation of fibromatous neoplasms arising from the connective tissue elements of the nerves, including, it has been claimed, the sheath of Schwann; and perhaps the rarity of growths in the central nervous system itself is due to the absence of this sheath in the medullated fibres of the white substance. According to some authors, neurofibromatosis may be occasionally associated with sclerotic or gliomatous patches in the central nervous system, but its association with tuberous sclerosis and with Pringle's telangiectatic type of so-called 'sebaceous adenomata' of the face must be exceedingly rare, if it occurs at all. Dr. Perdrau once examined the kidneys from an undoubted case of tuberous sclerosis of the brain, and they contained true neurofibromata (6). The following are the chief component signs of the disease, most of which are directly due to the neurofibromatous process.

The Cutaneous Pigmentation.

This is often the earliest sign of the disease, and is present in nearly all cases. It usually takes the form of greyish-brown, *café-au-lait*, spots and patches, of various shades, sizes, and numbers, distributed especially over the trunk. To these may be added much darker spots, and occasionally there may be symmetrical sheet-like pigmentation, not very dark, of large areas, as the face ('facies faunica') or neck and shoulders. The pigmentary 'formes frustes' of Recklinghausen's disease are in reality mostly early stages, developing later into the fully developed disease. Thus, a girl, aged 14 years, whom I described in 1905 as a case of 'Unusual Cutaneous Pigmentation possibly allied to Recklinghausen's Disease', in addition to scattered *café-au-lait* and darker spots had diffuse sheet-like pigmentation of the upper part of the back and neck, well seen in the drawing by Miss Mabel Green reproduced with a later account published in 1909 (see Pl. 6, Fig. 3). When she was examined again, in 1926, after she had been married for some years and had a child, she was a characteristic example of Recklinghausen's disease (Pl. 6, Fig. 4), with the usual pigmentation and 'molluscous' fibromata and a diffuse, soft, cushion-like mass in the subcutaneous tissue of the outer part of the right thigh, and a slightly tender swelling on the right side of the lower part of the neck, probably connected with a nerve-trunk (7).

Soldan (8) concluded that the cutaneous pigment-spots in Recklinghausen's disease were probably a direct result of the neurofibromatous process in the cutaneous nerves, but this is very doubtful. The congenital examples seem to be indistinguishable from ordinary simple pigment-naevi.

The Cutaneous Fibromata.

The 'molluscous' fibromata are so well-known that they need no elaborate description, and indeed they used to be known long ago as multiple 'molluscous

tumours of the skin '. They are situated chiefly on the trunk, and in number they vary from a few to many hundreds, and in size from miliary to larger than an orange. In the illustration (Pl. 6, Fig. 5) from the photograph of a woman (Mrs. M. K.), aged 40 years, some fairly large molluscous fibromata are seen on the left upper arm. They may be scarcely raised or much raised, sessile or pedunculated. Those with a thin pedicle are said occasionally to drop off spontaneously. They are formed from the connective tissue elements of the small cutaneous nerves, as the tumours of the deeper nerve-trunks are from the endoneurium, perineurium, or epineurium, or sheath of Schwann. It is not to be wondered at that nerve-fibres may be occasionally included or carried into all kinds of neurofibromata, but in those of young patients it seems that newly-formed nerve-fibres have occasionally been found. In two or three cases with multiple scattered peripheral tumours clinically resembling Recklinghausen's disease, microscopic examination of the tumours has shown them to be gangli-neuromata (Lhermitte and Dumas). In consistence the cutaneous neuro-fibromata are mostly soft, as the adjective 'molluscous' (*mollis* = soft) implies, but vary considerably; some of them undergo a myxomatous change and become so soft and atrophic that they resemble a shrivelled grape in appearance; sometimes even on palpation they seem to form cavities in the skin im-perfectly filled with fluid, into which the finger-tip can easily be pressed, so that they are reminiscent of some of the spots met with in cases of 'macular atrophy' of the skin. Whether the so-called multiple benign cutaneous tumours of Schweniger and Buzzi are atrophic forms of molluscous fibromata is doubtful.

Just as one or two congenital simple pigment naevi exactly resembling the ordinary pigment spots and patches of Recklinghausen's disease are so frequently met with in ordinary healthy persons as hardly to constitute an abnormality, so I believe that the presence of one or two small molluscous fibromata is not at all rare in otherwise normal persons.

There is no doubt that sudden aggravation of the manifestations of Recklinghausen's disease may be due to metabolic or endocrine factors, especially pregnancy, so that indeed it sometimes seems as if the onset of molluscous fibromata were due merely to pregnancy. They were said to have gradually appeared after typhoid fever, at the age of 18 years, in the case of a woman already referred to (Pl. 6, Fig. 5). Some that have appeared during pregnancy have disappeared after pregnancy (9). Some also may atrophy or practically dis-appear independently of pregnancy. Though the manifestations of neurofibro-matosis are largely influenced by endocrine factors, it seems to me that it would be quite wrong to conclude, as some have apparently done, that neurofibroma-tosis is a disease of endocrine origin. Various endocrine symptoms have, it is true, been observed in patients with undoubted neurofibromatosis, symptoms of Addison's disease in a few cases, symptoms of acromegaly or incomplete Fröhlich's syndrome, of precocious or retarded sexual development or dwarfism, and of thyroidal disturbance—but even so it must be remembered that the sella

turcica or pituitary gland might conceivably be directly affected by the neuro-fibromatous process, just as neurofibromatous filaments have been found, though rarely, in the suprarenal gland when symptoms of 'Addisonism' had been noted (10).

Neurofibromatosis of Nerve-trunks.

This is a graver, and sometimes a later, manifestation of the disease. In the most typical cases one or more, sometimes several, of the nerve-trunks can be felt to be affected, especially by palpitation of the extremities and sides of the neck. Along the course of the affected nerves there are one or more, often several, bead-like nodules, which may distend the nerve, affect one side of it, or be loosely attached to its sheath; in the neck such movable nodules may be mistaken for enlarged lymphatic glands; or the whole nerve may be uniformly or irregularly thickened by an interstitial neurofibromatosis for a variable length. It might even be suspected that the diagnosis of familial chronic hypertrophic interstitial neuritis had been made in such cases, but the thicken-ing is likely to be much greater than in the 'hypertrophic neuritis' cases, which are probably still rarer. The diffuse or beaded neurofibromatous thickening of nerve-trunks in the extremities is rarely visible on mere inspection, well illus-trated in the great monographs of R. W. Smith (1849) and Alexis Thomson (1900). More centrally situated tumours on the roots of the spinal and cranial nerves and on the cauda equina are a feature of some cases. Neurofibromata of the acoustic nerve and others in the ponto-cerebellar groove, in the absence of generalized neurofibromatosis, like isolated neurofibromata elsewhere, constitute a somewhat special class. The more centrally situated neurofibromata of the nerve-trunks are doubtless more likely to undergo malignant sarcomatous change than the cutaneous neurofibromata, but they may also mechanically injure the central nervous system and even penetrate into it.

Plexiform Neuroma, 'Elephantiasis Nervorum', Pachydermatocele, &c.

The condition known as plexiform neuroma is an exaggeration of the more diffuse neurofibromatosis of nerve-trunks mentioned above. It is mostly subcutaneous. It may occur in one half of the tongue and constitute the condition which Shattock termed 'hemimacroglossia neurofibromatosa' (11). When it is subcutaneous the thickened nerve-cords are sometimes felt sur-rounded by much loose fibrous tissue (12). Sometimes the loose fibrous tissue forms the chief part of a subcutaneous and cutaneous swelling, in which en-larged neurofibromatous nerves can be felt. Thus the condition is allied to the diffuse swelling known as pachydermatocele or 'chalastodermatocele'; and pachydermatoceles, the flounce-like or fold-like tumours ('Lappen-Elephan-tiasis') and pendulous tumours of the same nature, merge into the condition of neurofibromatous 'elephantiasis'. In fact, all these conditions have been some-times loosely spoken of as localized forms of 'elephantiasis'—that is to say,

'elephantiasis nervorum'. Probably the periosteum in the neighbourhood of such diffuse 'elephantiastic' swellings (13) is often also neurofibromatous and thickened, and then the bone under the periosteum is likely to be hyperplastic. Anyhow, there are many accounts of cases of irregular cranial hyperostosis associated with plexiform neuroma or the allied condition of pachydermatocele (14).

Neurofibromatosis of the Mucous Membranes, Viscera, and Sympathetic and Parasympathetic Nerves (15).

It will be sufficient here to mention that in rare cases neurofibromata have been found in the mucous membranes, as in the skin. In rare cases also neurofibromata have been detected in various viscera; there were several small neurofibromata on the peritoneal surface of the ileum in the case we shall describe farther on. It seems that visceral neurofibromata are especially liable to undergo a sarcomatous change.

The vagus and sympathetic nerves (16) may be affected, including probably the periarterial nerve plexuses supplying the limbs, a possible explanation of circulatory disturbances in the extremities met with in very rare cases of neurofibromatosis.

The Osseous and Periosteal Manifestations of Neurofibromatosis.

I need not again allude to the many various bony congenital abnormalities and malformations which have been occasionally met with in connexion with neurofibromatosis, nor need I mention the changes due to acromegaly in the very rare cases in which acromegaly has been associated with Recklinghausen's disease.

In a considerable proportion of the subjects of Recklinghausen's disease there has been scoliosis or kyphosis or kypho-scoliosis. Pelvic deformity due to bone-softening has also been observed. Gould (17), from a rather limited anatomical and histological examination of such cases, came to the conclusion that the bone-softening was microscopically and macroscopically indistinguishable from that of osteomalacia. But if this conclusion is correct it does not necessarily follow that some affection of the endocrine glands is the primary cause of the phenomena of Recklinghausen's disease. It must not be forgotten that spinal curvature is relatively quite as frequent, probably more frequent, in cases of syringomyelia where local bone-softening is probably also the cause, and yet no one suggests that the primary cause of syringomyelia is to be found in the endocrine glands. Moreover, neurofibromata of the roots of spinal nerves might in some cases be conceivably a cause of the spinal curvature—there might even be a congenital vertebral malformation, or there might be, though I think this unlikely, a local periosteal neurofibromatosis of vertebrae, as suggested by Brooks and Lehman (18). Their work constitutes a most

important advance in the understanding of the bony changes met with in neuro-fibromatosis.

These authors made a careful examination in seven cases of Recklinghausen's disease with bone changes. In their Case 2, a boy, aged 12 years (Pl. 7, Fig. 6), there was a condition of 'neurofibromatous elephantiasis' of the left leg, and the left tibia was longer than the right one. In their Case 6, a boy, aged 9 years, the left thigh was longer than the right one and showed an area of 'neuro-fibromatous elephantiasis'. In Lehman's Case 8, a woman, aged 30 years (Pl. 7, Fig. 7), the enlargement of the right lower limb was very striking. Amongst their chief findings by X-ray examination was the presence of local bone changes, which in the radiograms resembled subperiosteal and cortical cysts. Some of these cysts were bridged over by a thin layer of bone, so that they could be termed cortical instead of subperiosteal. Some of them could not have been felt by ordinary palpation, but others formed tumours projecting from the bone.

Their explanation of the changes, if I may express it in slightly different terms to those used in their description, is that when a periosteal nerve becomes neurofibromatous a certain amount of reaction is set up, as if by an infection, and processes of bone destruction and regeneration follow. If actively bone-forming periosteum covers the neurofibromatous tumour, a thin shell of bone is formed over the tumour, which then appears in the radiogram as a sub-periosteal bone-cyst. If the tumour growth farther invades the shaft of the bone and is associated with more active circulation of lymph and blood, the whole bone becomes more porous and plastic. This may of course lead to increase in length of the bone and to bending, or to irregularity if the neuro-fibromatous process is irregular, and, if a neurofibroma is so placed as to destroy an epiphysis, an abnormally short bone may result (19). They compare the process to what happens in chronic inflammatory conditions in growing bones. Brooks and Lehman were apparently the first to draw attention to the occurrence of periosteal neurofibromatosis and its results. Similar conditions have since then probably been seen by others, even if not interpreted in the same way (20). In Puech's account of the osseous manifestations in neurofibromatosis, published in 1925, no mention is made of periosteal neurofibromatosis (21). It is interesting that in one of Lehman's later cases (22), a woman of 30 years, in whom there was neurofibromatous 'elephantiasis' of the right lower extremity with overgrowth of the right innominate bone, there was also a neurofibromatous pelvic tumour.

The Present Case.

When there is a diffuse mass of neurofibromatous periosteum covering a considerable area of bone we doubt whether actual penetration of the neuro-fibroma into the osseous cortex is necessary to give rise to hyperplasia in the under-lying bone. In the following case a diffuse mass of thickened neurofibromatous periosteum covered the left tibia, which was greatly thickened and curved,

but there was no evidence that the neurofibromatous growth had actually penetrated into the cortex of the bone. We are indebted to Dr. G. F. Stebbing, of the Lambeth Hospital, for clinical notes of the case, and to Mr. Cecil Beadles and Mr. T. W. P. Lawrence for the macroscopic and microscopic description of the specimens in the Museum of the Royal College of Surgeons, to which Dr. Perdrau presented them.

The patient, a woman (F. L. G.), aged 47, a subject of typical Reckling-hausen's neurofibromatosis, was admitted on January 25, 1921, to the Lambeth Hospital on account of a severe accidental head injury causing a cerebral abscess, from the results of which she died on February 28, 1921. It was also noted that her left tibia was considerably curved, in no way connected with the accident, and that she had many molluscous fibromata of the skin. No family history or past history bearing on the latter condition was obtained. At the post-mortem examination, apart from the results of the accident from which she died, Dr. Perdrau noted:

'There are typical pedunculated and sessile molluscous tumours on the skin, most on the trunk, but also on all four limbs and face. The largest is pigmented, of the size of a golf-ball; the others are not pigmented, but there are spots and patches of pigmentation, especially on the trunk and thighs. There are no tumours in the central nervous system or on any nerve-trunks. There are a few small hard tumours on the peritoneal surface of the ileum, opposite the mesenteric attachment, varying in size from a sago-grain to a coffee-bean. There are no tumours elsewhere in the internal organs (heart, liver, kidneys, &c.) excepting a doubtful one at the tip of the vermiform appendix (23). The left tibia is deformed and bent, and is covered over the greater part of its length anteriorly with diffuse tumour-substance resembling the semi-transparent fibromata of the skin, but of denser texture. The tibia of the other leg is not bent.'

The specimens mounted at the Royal College of Surgeons are described as follows:

No. 3,816. 1. The left fibula and outer half of the tibia from a case of Recklinghausen's disease. The upper three-quarters of the anterior surface of the shaft of the tibia is covered with a layer of dense fibrous tissue, $\frac{1}{2}$ inch in thickness at its middle and becoming thinner above and below. The margin of the deposit is well defined; and its deep surface is in contact with the bone, from which it is readily detachable. In the section, in addition to the localized mass described, almost the whole of the periosteum of the shaft exhibits a thickening of similar character, but less marked. The bone adjacent to the deposit presents considerable thickening of its cortex and irregularity of its surface, which, however, is quite smooth. The tibia measures $14\frac{1}{2}$ inches in length and it and the fibula exhibit a uniform curve with the convexity outwards. (Pl. 7, Fig. 8, and Pl. 8, Figs. 9 and 10.)

No. 3,816. 2. The inner half of the left tibia from the same case. It shows similar changes, the fibrous thickening of the periosteum forming a thick coating over the greater part of the shaft of the bone.

Microscopic examination of the deposit on the bone shows it to consist of dense fibrous tissue, with abundant cellular elements, the cells being of small size and oval in form. In places the cells form narrow tracts in which the fibrous element is almost absent. The structure is similar to that of the fibro-mata of the skin from the same case (which are preserved as No. 3,074. 2), but a few thickened nerves are present.

No. 3,074. 2. Two pieces of skin from a case of Recklinghausen's disease. A number of firm fibromata, varying from miliary size to one inch in diameter,

project from the surface. Some of the smaller nodules are surrounded by a narrow zone of brown pigmentation, and small areas of pigmentation are scattered throughout the surface of the skin.

Microscopic examination shows that the tumours of the skin are fibromata; their outlines are well defined, but no capsule is present. The texture is dense, but the cellular element is abundant, the cells being of small size and oval in shape. The corium is somewhat sclerosed, and many of the blood-vessels of the papillary layer are surrounded by a narrow layer of small oval cells.

In addition to these specimens, Dr. Perdrau has excellent microscopic sections of the thickened (neurofibromatous) periosteum, of one of the cutaneous fibromata and of one of the small tumours from the ileum. The microscopic structure of the last resembles that of the others. They all show typical neurofibroma, as the microscopical sections in the Royal College of Surgeons do, in fact, in microscopical structure the various tumours examined are exactly alike (Pl. 9, Figs. 11, 12, and 13). Dr. Perdrau also has sections of the tumours from all three localities stained by the silver reduction method for reticulin, a method which he described some years ago (24) for the differentiation of 'reticulin' from glia-fibres, axis cylinders, &c. Sections of all three tumours stain equally well for reticulin by this method.

Remarks.

With the exception of important observations by Brooks and Lehman, this seems to be the first account explaining the deformity of an extremity or other part, for instance, the skull, as due to periosteal neurofibromatosis, with resulting abnormal thickness or hyperplasia of the underlying bone. The increased bone-formation may be accounted for by comparison with the increased length of long bones caused by chronic osteomyelitis in youth, as pointed out by Brooks and Lehman, or long-continued chronic ulceration, which causes periosteal hyper-aemia. As an illustration we figure the case of a boy whom I used frequently to see when, in 1897, at the age of 14 years, the boy was an in-patient at the German Hospital. The photograph (Pl. 7, Fig. 14) was taken at that time by Dr. J. P. zum Busch, to whom I am indebted for it. The extraordinary length of the boy's legs was due to the abnormal hyperaemia caused by chronic con-genital syphilitic osteo-periostitis (25). One might here also call to mind the group of cases described by Parkes Weber as manifesting haemangiectatic hyper-trophy of a limb due to excessive blood-supply of congenital-developmental origin (26).

The present case is not really unique. Besides cases figured and described by Brooks and Lehman, there are various descriptions to be found in the literature on neurofibromatosis in which one of the patient's limbs was thicker and longer than its fellow. These have mostly been classified as examples of neurofibromatous elephantiasis' when they showed a condition of extensive plexiform neuroma or pachydermatocele of the subcutaneous tissues, but in some such cases the hypertrophy or bending of the bone was probably due to overlying periosteal neurofibromatosis, similar to that described in the present paper. A leg amputated above the knee, recently presented by Dr. Maud Forrester-Brown to the Museum of the Royal College of Surgeons in London,

showed decided increase in length as compared with its fellow, and a condition of diffuse neurofibromatous 'elephantiasis'; in addition, there was moderate but diffuse neurofibromatous thickening of the periosteum of the shafts of the tibia and fibula (specimens 5090. 5–8).

The famous 'elephant man' (Merrick), whom I once saw, and who died at the London Hospital (27) at the age of 27 years, on April 11, 1890, had many deformities of the nature of pachydermatoceles as well as many bony thickenings and outgrowths. There was no post-mortem examination, but irregular periosteal neurofibromatosis may well have played a part in his osseous deformities.

Further Observations.

In connexion with the various points on neurofibromatosis considered or alluded to in this paper, I venture to make the following short pathological and diagnostic summary :

1. It is quite common in the course of ordinary medical examinations to meet with one or two simple pigmentary or hyperchromic nævi indistinguishable from the cutaneous pigment spots of Recklinghausen's disease, and to meet with one or two little molluscous fibromata of the skin. These have no importance unless in association with other signs. When, however, it is a question of the nature of a chronic non-inflammatory swelling in one half of the tongue, or of a loose fold of superabundant skin and subcutaneous tissue over one eye or at the side of the head, they have a significance in favour of neurofibromatosis as an explanation of the condition.

2. The prognosis in a case of supposed pigmentary 'forme fruste' of Recklinghausen's disease in a child or young person should be very guarded. Most cases develop later into 'full-blown' neurofibromatosis. In young women pregnancy, and probably also the onset of puberty, may act as an excitant in the development of molluscous fibromata, &c.

3. The tumour-like swellings due to plexiform neuroma, and those which have been described as elephantiasis nervorum, merge into pachydermatocele and 'molluscous' subcutaneous fibromatous pendulous tumours and flounce-like folds. Changes of the kind have often been called elephantiasis (neurofibromatosa), since the term 'elephantiasis' was formerly applied to any chronic deforming and unsightly enlargement of an extremity or other part of the body. The term 'dermatolysis', or 'dermolysis', looseness or loosening of skin, should be avoided in regard to pachydermatoceles and the kindred folds, as it leads to confusion with the very rare condition of congenital generalized 'elastic skin', in which the skin is abnormally loosely attached to the parts beneath it (28), so that the skin of the chest, for instance, can be drawn out in a fold to cover the face, but when released, at once, owing to its inherent, normal or over-normal, elasticity, retracts to its natural position.

4. Tumour-like swellings of the above 'elephantiastic' class, including true

plexiform neuroma, pachydermatocele, diffuse 'molluscous' subcutaneous connective tissue tumours and 'folds' are often associated with hyperostosis (hyperplasia) of the underlying bones, whether of the limbs or head or elsewhere. There has been great confusion in regard to the explanation of the cranial deformities sometimes associated with such neurofibromatous swellings and pachydermatocele 'folds' of the face and scalp, and likewise, with regard to the association in other parts of 'elephantiastic' swellings with local osseous hyperplasia.

5. In the above-described case of the woman, F. L. G., the osseous hyperplasia of the left tibia was associated with irregular diffuse neurofibromatous thickening of the periosteum covering it, and with bending of the shaft of the bone. It remains to be seen how often a similar condition of neurofibromatous diffuse thickening of the periosteum will be found in cases of gross osseous hyperplasia and deformity of an extremity, or of the face or skull, in cases of neurofibromatosis. The description by Brooks and Lehman of subperiosteal and cortical 'cysts' and other changes in the bones found by X-ray examination in cases of neurofibromatosis constitutes a landmark in the history of our knowledge of the subject.

6. As causes of chronic thickening of nerve-trunks, besides leprosy, there are two of congenital developmental nature: (a) the exceedingly rare familial 'hypertrophic neuritis', in which the thickening is said to be of the sheath of Schwann (29); (b) diffuse neurofibromatosis of nerve-trunks. The latter, which is only a diffuse and more generalized variety of multiple neurofibromata (discrete neurofibromatous tumours) of nerve-trunks, may be very widely distributed; it may affect not only the spinal nerves of the extremities, body and neck and probably the head, but also the sympathetic and vagus nerves and the visceral nerve plexuses, e. g. about the heart and aorta.

7. Amongst the causes of enlargement, notably in bone-length, of a single extremity, two rare causes of a congenital-developmental nature should be better recognized: (a) the haemangiectatic hypertrophy of an extremity (Parkes Weber), already alluded to (26), and (b) the enlargement due to neurofibromatosis. The latter is generally accompanied by plexiform neuroma or neurofibromatous pachydermatocele of the soft parts of the extremity; both plexiform neuroma and pachydermatocele, when in extreme degree, are often spoken of as neurofibromatous elephantiasis; but it will probably be found that more or less diffuse neurofibromatous thickening of the periosteum is nearly always likewise present in these cases to account for the bony hyperplasia, as it was in the amputated leg, to which I have already referred under 'Remarks'.

In cases of both these rare classes the bony hyperplasia is probably intimately connected with excessive blood-supply. In the haemangiectatic cases the increased blood-supply is the direct result of the primary vascular abnormality; in the periosteal neurofibromatous cases it is secondary and possibly a reactionary manifestation, as it, of course, is in the cases of syphilitic hypertrophy of extremities to which I have alluded.

8. Besides syphilis, tuberculosis, and leprosy, three possible, though rare, causes of chronic periosteal thickening should be remembered:

(A) Secondary osteo-arthropathy of Pierre Marie. The periosteal thickening in these cases commences in and affects especially the terminal portions of the extremities, notably the phalanges and metacarpal and metatarsal bones. It is always accompanied by clubbed fingers.

(B) Periosteal lymphogranulomatosis. This is apparently limited to the vertebral column, and is probably of more frequent occurrence than has been suspected in late cases of lymphogranulomatosis maligna (Hodgkin's disease), especially when the para-aortic and retroperitoneal lymphatic glands are much involved. Clinically, its presence should be suspected in such cases when bilateral radiating lumbar and sciatic pains are complained of, and, of course, when paraplegic symptoms are commencing, which may be asymmetrical at first. The lymphogranulomatous periosteal thickening seems to commence symmetrically in front of or at the sides of the bodies of the vertebrae about the level of the diaphragm and then tends to spread round so as to involve the spinal canal and the epidural fat. It has been specially considered by me in connexion with the occurrence of cauda equina symptoms and paraplegia in Hodgkin's disease (30). Incidentally, the lymphogranulomatous process, like the neurofibromatous process, may become sarcomatous (31).

(C) Periosteal neurofibromatosis, which has constituted the main subject of the present paper. Although undoubtedly it was present in some earlier reported cases, it was hardly recognized as such, if recognized at all, until Brooks and Lehman drew attention to the subject in 1924 and recognized its pathological and clinical interest and importance. As I have endeavoured to explain in this paper, more or less periosteal neurofibromatosis is probably present in all the cases roughly grouped together as neurofibromatous elephantiasis (compare conclusions 4 and 5) of limbs, especially those which show definite excess in bone-length. Such cases are apparently nearly always unilateral.

REFERENCES AND NOTES

1. Von Recklinghausen, 'Ueber die multiplen Fibrome der Haut', Berlin, 1882. The monographs by A. Thomson (1900) and C. Adrian (1903) constitute landmarks in the literature of the subject. Robert W. Smith described and admirably illustrated generalized neurofibromatosis in his *Treatise on the Pathology, Diagnosis, and Treatment of Neuroma*, Dublin, 1849 (cf. J. F. Fulton, *New England Journal of Medicine*, Boston, 1929, cc. 1315).

2. Adrian, C., *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.*, Jena, 1903, vi. 465, 514; A. Puech, 'Les manifestations osseuses dans la neurofibromatose', *Paris Méd.*, 1925, lvii. 502; Laignel-Lavastine and Valence, *Bull. et Mém. de la Soc. méd. des hôp. de Paris*, 1926, Ser. iii. 1. 273.

3. Brooks, B., and Lehman, E. P., 'The Bone Changes in Recklinghausen's Neurofibromatosis', *Surg., Gynecol., and Obstet.*, Chicago, 1924, xxxviii. 587–95, Case 4. Laignel-Lavastine and Dauptain (*Bull. et Mém. de la Soc. méd. des hôp. de Paris*, 1924, Ser. iii. xlviii. 1163) recorded the case of a man, aged 37 years, with typical complete Recklinghausen's disease and a spina bifida occulta in the lumbar region; his daughter had a pigmentary incomplete form of the disease.

4. Weber, F. Parkes, 'Cutaneous Neurofibromatosis, with a Left Lateral (Suprazygomatic) Meningocele', *Proc. Roy. Soc. Med., Clin. Sect.*, Lond., 1925, xviii. 1–4. At first sight the meningocele in this case simulated a soft fibromatous fold of skin of the nature of a 'pachydermatocele', sometimes met with in cases of neurofibromatosis.

5. See Weber, F. P., 'The Relations of Capillary Haemangiectatic Naevus and Naevus Anaemicus to the Nervous System', *Brit. Journ. Derm. and Syph.*, 1929, xli. 221. In regard to abnormal conditions of the eye in neurofibromatosis, see T. Van der Hoeve, 'Eye Diseases in Tuberose Sclerosis of the Brain and in Recklinghausen's Disease', *Trans. Ophthalm. Soc. United Kingdom*, Lond., 1923, xliii. 534, and H. Fischer, *Dermat. Zeitschr.*, Berlin, 1924, xlii. 143–68.

6. In regard to the possible relation of neurofibromatosis to sclerotic or gliomatous patches in the central nervous system and tuberous sclerosis, see Cristin, E., and Naville, F., 'À propos des neurofibromatoses centrales', *Annales de Méd.* Paris, 1920, viii. 30–50 ; also the following articles, for reference to which I am indebted to Dr. Macdonald Critchley : Gamper, E., *Journ. f. Psych. u. Neurol*, Leipz., 1929, xxxix. 39 ; Bielschowsky and Rose, *ibid.*, 1928, xxxv. 42 ; Bielschowsky, 'Ueber tuberose Sklerose und ihre Beziehungen zur Recklinghausenschen Krankheit', *Zeitschr. f. d. ges. Neurol. u. Psych.*, Berlin, 1914, xxvi. 133 ; Orzechowski and Nowicki, 'Neurofibromatose und Sclerosis tuberosa (Neurofibromatosis universalis)', *ibid.*, 1912, xi. 237 ; Schnyder, P., 'Ueber Gliom, Gliose und Gliomatose und ihre Beziehungen zur Neurinomatosis', *Schweizer Arch. f. Neurol. u. Psych.*, Zürich, 1928, xxiii. 116.

7. Weber, F. Parkes, *Brit. Journ. Dermat.*, Lond., 1905, xvii. 226 ; *ibid.*, 1909, xxi. 49 ; *Proc. Roy. Soc. Med., Sect. of Derm.*, 1927, xxx. 22. For many references to the literature on 'Pigmentary Incomplete Forms of Recklinghausen's Disease' see Weber, F. P., *Med. Press and Circ.*, Lond., 1925, clxx. 416–19. See also Wise, F., and Eller, J. J., *Journ. Amer. Med. Assoc.*, Chicago, 1926, lxxxvi. 86, and Eller, J. J., *Arch. Derm. and Syph.*, *ibid.*, 1928, xvii. 648.

8. Soldan, 'Ueber die Beziehungen der Pigmentmäler zur Neurofibromatose', *Arch. f. klin. Chir.*, Berlin, 1899, lix. 261–96.

9. Cf. Sutton, R. L., 'Fibroma Molluscum Gravidarum', *Amer. Journ. Med. Sci.*, Philad., 1914, cxlvii. 419.

10. For many references on the association of Recklinghausen's disease or one of its incomplete forms with acromegaly, Addison's disease, or an incomplete form of dystrophia adiposo-genitalis (Fröhlich's syndrome), and on Leschke's 'dystrophia pigmentosa', see Weber, F. P., *Med. Press and Circ.*, Lond., 1925, clxx. 416–19.

11. See Abbott and Shattock, *Trans. Path. Soc. Lond.*, 1903, liv. 231 ; Spencer and Shattock, *Proc. Roy. Soc. Med., Sect. Path.*, Lond., 1908, i. 8 ; Weber, F. P., 'Neurofibromatosis of the Tongue', *Brit. Journ. Child. Dis.*, Lond., 1910, vii. 13 ; Oddy, H. M., *Proc. Roy. Soc. Med., Sect. Study of Dis. in Children*, Lond., 1929, xxii. 93. See also Hayashi, A., 'Makroglossia congenita neurofibromatosa', *Deut. Zeitschr. f. Chir.*, Leipz., 1912, cxviii. 456, and the cases quoted by him. On the analogous condition in the *lip* ('hemimacrocheilia neurofibromatosa') see Rolleston, J. D., and Macnaughtan, N. S., *Proc. Roy. Soc. Med., Clin. Sect.*, Lond., 1911, iv. 114. In neurofibromatous hypertrophy of half of the tongue nerve-cords are not always distinctly felt—cf. W. Russell Brain's case (which I had the privilege of examining), reported in *Brain*, Lond., 1928, li. 113. Some cases of diffuse bilateral or unilateral hypertrophy of *gums* are doubtless of neurofibromatous nature (though not plexiform neuroma), at least the hereditary ones, such as those in the group of familial molluscous fibromata cases described firstly by John Murray in 1873 (*Med.-Chir. Transactions*, Lond., 1873, lvi. 235) and later by Whitfield, A., and Robinson, A. H. (*ibid.*, 1903, lxxxvi. 293). On this subject compare also the cases of 'unilateral hypertrophy of gums associated with other abnormalities' collected by Sir G. M. Humphry, in 'Selected Essays and Monographs', New Syd. Soc., Lond., 1901, clxxiii. 229–36. In the case of a boy, aged seven years, described by Marfan, A. B., and Schmite under the heading, 'Adéno-lymphocèles et lymphangiomes congénitaux avec taches pigmentaires généralisées sans molluscum et sans neurofibromes' (*Bull. de la Soc. de Pédiatrie de Paris*, 1926, xxiv. 269), I would suggest that the right-sided hemi-hypertrophy of the tongue was more probably of neurofibromatous than of lymphangiomatous nature. See Gray, A. M. H., *Proc. Roy. Soc. Med., Sect. Derm.*, Lond., 1929, xxii. 38 ; the patient, a boy aged 15 with

Recklinghausen's neurofibromatosis, had a great nodular enlargement of the median and ulnar nerves in both arms.

12. Cf. A. E. Barker's case, *Trans. Med. Soc. Lond.*, 1912, xxxv. 376. I was able to palpate the swelling myself on two occasions. See also Bell, G., and Inglis, K., *Med. Journ. Australia*, 1925, ii. 423, a case of plexiform neuroma associated with true gigantism of one finger.

13. In regard to the adjective 'elephantiastic' or 'elephantiasic' cf. Esmarch and Kulenkampff's monograph, *Die elephantiastischen Formen*, Hamburg, 1885.

14. Compare remarks by Weber, F. P. on a complicated case of neurofibromatosis with asymmetrical facial hyperostosis shown by W. Russell Brain at the Neurol. Sect. of the Roy. Soc. Med. on November 10, 1927, as reported in *Brain*, Lond., 1928, li. 113. Various of the earlier cases of neurofibromatosis associated with partial cranial hyperostosis were referred to in a paper by Weber, F. P., *Brit. Journ. Child. Dis.*, Lond., 1910, vii. 13-16. Authors have mentioned and discussed not only the irregular areas of cranial hyperostosis sometimes connected with neurofibromatous conditions of the soft parts covering them, but also patches of thinness or local atrophy or decalcification that have occasionally been demonstrated by X-ray examination of the skull in patients with Recklinghausen's disease. Cf. Brooks and Lehman (1924), and Lehman (1926), both referred to further on, and Stahnke, E., *Deut. Zeitschr. f. Chir.*, Leipz., 1922, clxviii. 6. On the whole subject of the cranial changes in neurofibromatosis and for references on the subject, see also Winkelbauer, E., *ibid.*, 1927, ccv. 230-57.

15. Cf. Banerjee, D. N., and Christeller, E., 'Ueber die gastro-intestinalen und andere seltenere Lokalisationen der Neurofibromatosis', *Virchow's archiv. f. Path. Anat. u. Physiol.*, Berlin, 1926, cclxi. 50-67.

16. In a case of generalized neurofibromatosis under Moynihan (*Lancet*, Lond., 1901, i. 28), there was a neurofibromatous tumour of the vagus nerve. In a case described by Preble, R. B., and Hektoen, L. (*Amer. Journ. Med. Sci.*, Philad., 1901, cxxi. 1) there were tumours of the vagus and cervical sympathetic nerves and their branches; in their illustration of the affected vagus and sympathetic nerves about the base of the heart and large vessels in the thorax a subpericardial neurofibromatous nodule is also shown. In an annotation in the *Lancet* (1929, ii. 1364) we read that amongst the recent additions to the Museum of the Royal College of Surgeons there are specimens of Recklinghausen's disease, illustrating the remarkable convoluted masses of enlarged nerves, and the extensive involvement not only of the peripheral nerves, but also of the great plexuses, the vagi and other cranial nerves, and the sympathetic nervous system. We find that the last specimens alluded to are Nos. 5090.1, 5090.2, 5090.3, and 5090.4 (all from one case and presented by the London School of Medicine for Women).

17. Gould, E. P., 'The Bone Changes occurring in von Recklinghausen's Disease', *Quart. Journ. Med.*, Oxford, 1918, xi. 221.

18. Brooks, B., and Lehman, E. P., 'The Bone Changes in Recklinghausen's Neurofibromatosis', *Surgery, Gynecology, and Obstetrics*, 1924, xxxviii. 587-95.

19. For references to older literature on the connexion of lengthening or shortening of extremities with neurofibromatosis, see Stahnke, 'Ueber Knochenveränderungen bei Neurofibromatose', *Deut. Zeitschr. f. Chir.*, Leipz., 1922, clxviii. 6.

20. Cf. Babonneix, Touraine, and Pollet, *Bull. et Mém. de la Soc. méd. des hôp. de Paris*, 1925, Series iii, xlix. 1601; Tixier (Lyon), report in *Presse médicale*, Paris, 1925, xxxiii. 1689; and other scattered observations.

21. Puech, A., *Paris médical*, 1925, lvii. 502.

22. Lehman, E. P., 'Recklinghausen's Neurofibromatosis and the Skeleton', *Arch. of Derm. and Syph.*, Chicago, 1926, xiv. 178.

23. Cf. Hoey, T., 'Recklinghausen's Disease associated with Fibroma of the Appendix', *Brit. Med. Journ.*, 1928, ii. 490.

24. Perdrau, J. R., *Journ. Path. and Bact.*, Edinb., 1921, xxiv. 117.

25. The case was described and figured by Mr. R. W. Parker in his article on 'Syphilis', in Gould and Warren's *International Text-book of Surgery* (1900, ii. 780), and was referred to by F. Parkes Weber, in 'A Note on Congenital Syphilitic "Osteitis Deformans",' *Brit. Journ. Child. Dis.*, Lond., 1908, v. 83. The patient, when seen by Dr. zum Busch, in 1913, sixteen

years after the photograph was taken, had no signs of active syphilis, but the bones were of course still somewhat deformed.

26. See Weber, F. Parkes, 'Haemangiectatic Hypertrophy of Limbs', *Brit. Journ. Child. Dis.*, Lond., 1918, xv. 13 ; Gray, A. M. H., 'Haemangiectatic Hypertrophy (Parkes Weber)', *Proc. Roy. Soc. Med., Sect. Derm.*, Lond., 1928, **xxi**. 65. Various other examples of this rare congenital developmental abnormality are referred to in these papers, and I have lately seen an account of the condition in France in which it is stated to be apparently commoner in England !

27. See the illustrations of the 'elephant man' in the *Brit. Med. Journ.*, 1886, ii. 1188; 1890, i. 916 ; 1923, i. 335. See also Treves F., 'A Case of Congenital Deformity', *Trans. Path. Soc.*, Lond., 1885, lxxxvi. 494.

28. See Weber, F. Parkes, 'Chalasodermia or Loose Skin', *Urologic and Cutaneous Review*, St. Louis (Missouri), 1923, xxvii. 407.

29. There are two types, that of Déjerine and Sottas and that of Pierre Marie. I saw one of Déjerine's original familial cases in Paris about 1923. Dr. Macdonald Critchley has pointed out to me that familial hypertrophic neuritis is pathologically related to neurofibromatosis, according to the work of Bielschowsky, *Journ. f. Psych. u. Neurol.*, Leipz., 1923, xxix. 182. Verocay, J. ('Zur Kenntnis der Neurofibrome', *Beitr. z. path. Anat. u. z. Allg. Path.*, Jena, 1910, xlviii. 1–69) thought that the tumours of Recklinghausen's disease, for which he suggested the term 'neurinomata', arose from the cells of the sheath of Schwann, but this view has been only partially accepted. Quite recently S. H. Gray, in a paper on ' The Histogenesis of Recklinghausen's Disease ' (*Arch. of Neurol. and Psych.*, Chicago, 1929, **xxii**. 91), for reference to which I am indebted to Dr. Perdrau, described two cases, in both of which a fibrosarcomatous change had occurred. In one of these cases serial microscopic sections showed the tumour arising not from the cells of the sheath of Schwann but from the perineural connective tissue.

30. Weber, F. Parkes, 'Paraplegia and Cauda Equina Symptoms in Lymphogranulomatosis Maligna', *Quart. Journ. Med.*, Oxford, 1923, xvii. 1–5 ; *idem.*, 'Paraplegia in Lymphogranulomatosis Maligna and Leukaemia', *International Clinics*, Philad., 1926, Ser. 36, i. 127–136 ; Weber and Bode, 'Abdominal Lymphogranulomatosis Maligna and Lymphogranulomatous Infiltration of the Epidural Fat', *Lancet*, Lond., 1927, ii. 806. Periosteal thickening of the vertebrae may, however, be present without cauda equina symptoms or paraplegia, and these latter symptoms may occur in cases of lymphogranulomatosis maligna without periosteal thickening—cf. above references, and also East and Lightwood, *Lancet*, Lond., 1927, ii. 807, and Carslaw and Young, *Glasgow Med. Journ.*, 1927, cviii. 193. For a somewhat analogous symmetrical periosteal elevation over various bones in lymphatic leukaemia and aleukaemic lymphadenosis (due to subperiosteal leukaemic infiltration), see Taylor, H. K., 'Periosteal Changes in a Case of Lymphatic Leukaemia', *Radiology*, 1926, vi. 523–5.

51. Cf. Weber, F. Parkes, 'La lymphogranulomatose maligne ou granulome de Hodgkin et la question du sarcome de Hodgkin', *Strassbourg médical*, 1926, lxxxiv. 255.

DESCRIPTION OF PLATES

FIGS. 1 and 2. Case of cutaneous neurofibromatosis. The patient has a meningocele on the left side of the face, resembling a soft fibromatous fold of skin or pachydermatocele, such as are occasionally met with in Recklinghausen's disease; there is a tuft of hair below it. (F. Parkes Weber, *Proc. Roy. Soc. Med., Clin. Sect.*, Lond., 1925, xviii. 1.)

FIG. 3. Recklinghausen's disease. A girl, with a pigmentary 'forme fruste', when seen in 1905, at the age of 14 years. This photograph was not illustrated in my published account of the case.

FIG. 4 *a* and *b*. Recklinghausen's disease. The same case in 1926, when fully developed, with numerous molluscous fibromata.

FIG 5. Recklinghausen's disease. A woman (Mrs. M. K.), aged 40 years, with some fairly large molluscous fibromata on the left upper arm. The photograph was taken in January 1904, and several years later (December 10, 1909), I showed the patient at the Clinical Section of the Royal Society of Medicine (*Proc. Roy. Soc. Med., Clinical Section*, 1909–1910, iii. 79), but my account was accompanied by a different illustration, showing the appearance of the patient's back. The molluscous fibromata were said to have gradually appeared after typhoid fever at the age of 18 years. There was typical, though relatively slight, cutaneous pigmentation.

FIGS. 6 and 7. Neurofibromatous elephantiasis and periosteal neurofibromatosis. Illustrations showing enlargement of one limb, from the articles by B. Brooks and E. P. Lehman (1924), and E. P. Lehman (1926), by their kind permission. Fig. 6 is Case no. 2 of Brooks and Lehman, a boy, aged 12 years, whose (affected) left leg is obviously longer than his right leg. Fig. 7 is Lehman's Case no. 8, a woman, aged 30 years, with enlargement of the right lower limb.

FIG. 8. The present case. Drawing by Mr. S. Steward from the left tibia and fibula (⅔ natural size) in the Museum of the Royal College of Surgeons (No. 3816.1), to show the periosteal thickening (periosteal neurofibromatosis) and the irregular hyperplasia of the cortical bone of the diaphysis of the tibia.

FIG. 9. The present case. Photograph of the left tibia and fibula before splitting the tibia, to show the curving of the bones and the great periosteal thickening over the upper part of the tibia. We are indebted for this photograph to the Department of Applied Optics, National Institute for Medical Research.

FIG. 10. The present case. Radiogram of the left tibia and fibula, taken after death, to show the bending of the bones and the great thickness, and consequent opacity, of the cortical bone of the main portion of the shaft of the tibia. We are indebted for this radiogram to the kindness of Dr. Russell Reynolds.

FIGS. 11, 12, and 13. The present case. Microphotographs ($\times 240$) from (Fig. 11) the thickened (neurofibromatous) periosteum over the left tibia, from (Fig. 12) one of the cutaneous neurofibromatous growths, and from (Fig. 13) one of the neurofibromatous growths of the ileum. Note the somewhat coarser structure in Fig. 11. We are indebted for these microphotographs to the Department of Applied Optics, National Institute of Medical Research.

FIG. 14. (For comparison.) Case of remarkable enlargement of the long bones of the legs, due to congenital syphilis. From a photograph taken in 1897, when the patient was aged 14 years. The forearms are similarly, but to a lesser degree, affected. This photograph, for which I am indebted to Dr. J. P. zum Busch (see text), is to contrast with cases of bony enlargement accompanying periosteal neurofibromatosis.
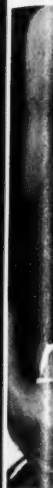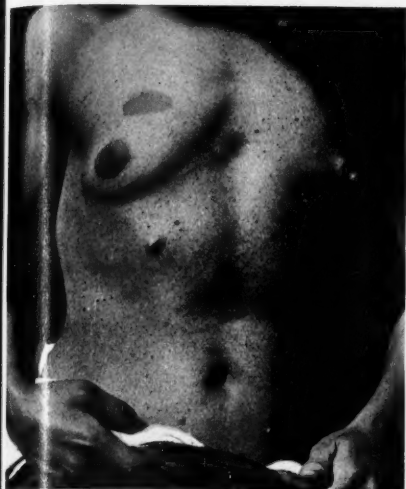
Fig. 1

Fig. 2

Fig. 4 *a*

Fig. 4 *b*

Fig. 3
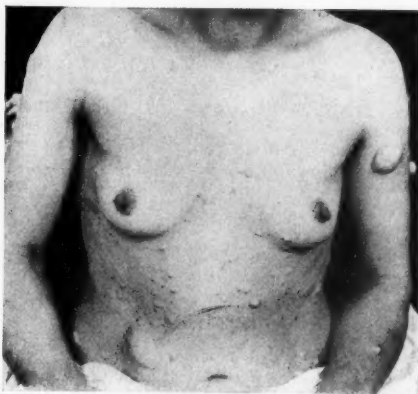
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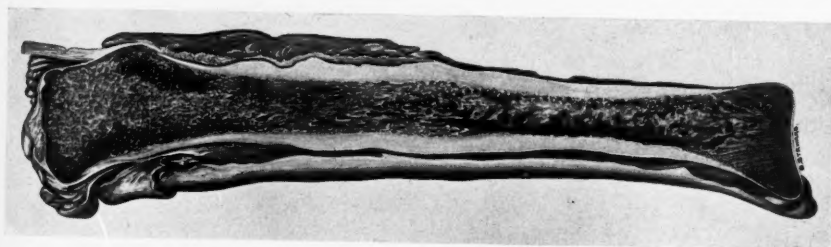
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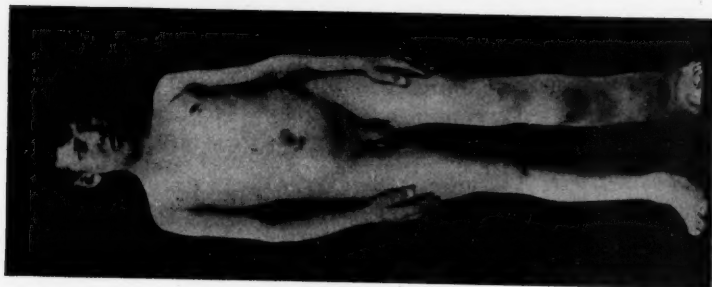
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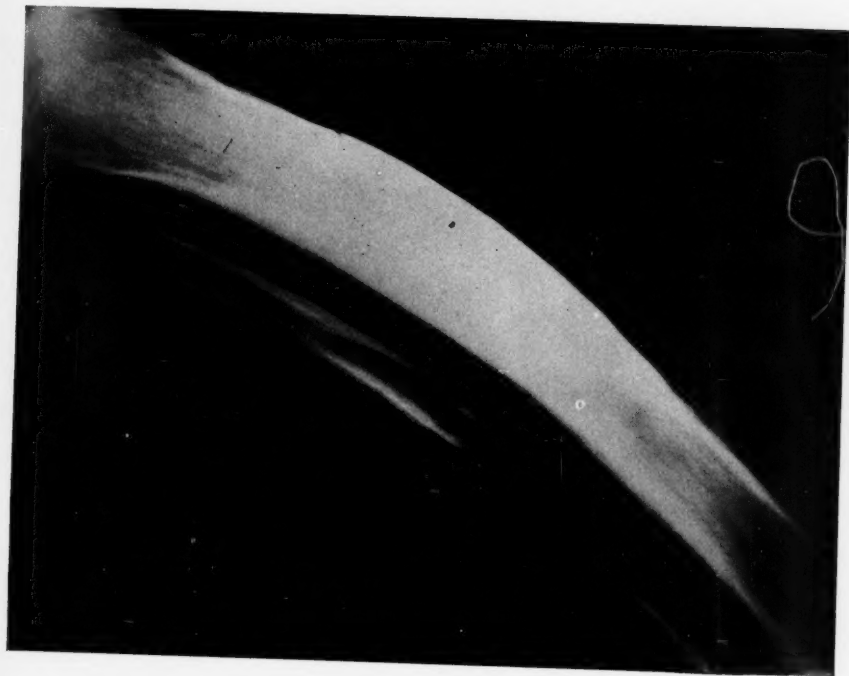
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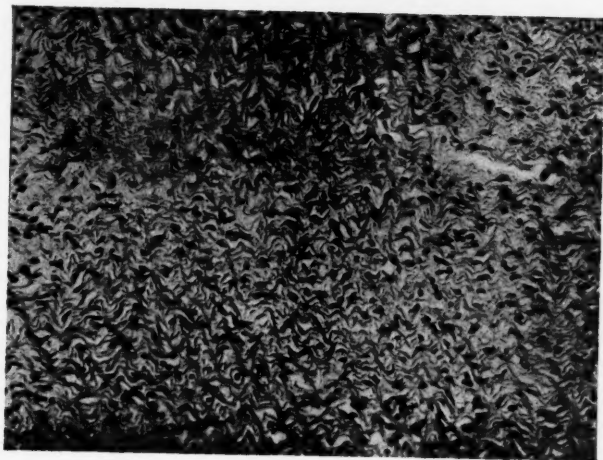
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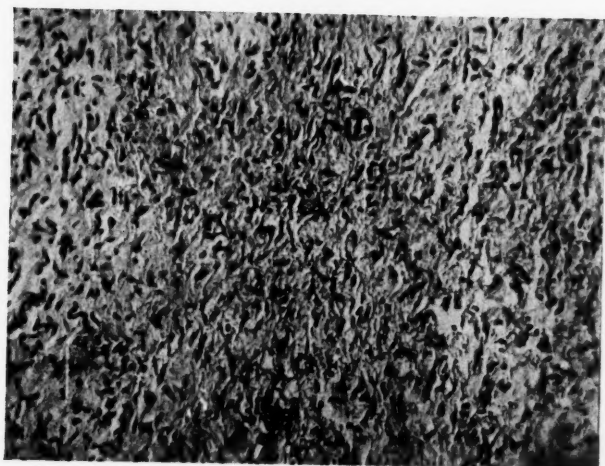
FIG. 12

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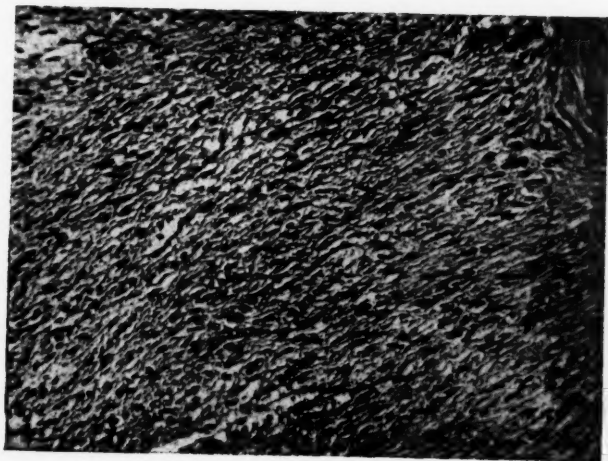
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A CLINICAL METHOD FOR THE CONTINUOUS REGISTRATION OF BLOOD-PRESSURE [1]

By F. L. GOLLA and S. ANTONOVITCH

(From the Central Pathological Laboratory of the London County Mental Hospitals)

With Plate 10

DURING the course of investigation into the organic resonance of affective states it became necessary to obtain continuous measurements of the systolic blood-pressure. The method to be described has yielded such satisfactory results that it has seemed to us worth the attention of clinical observers, as a possible procedure in the investigation of vascular and cardiac disease

The only method hitherto devised which claims to give a continuous record of the systolic blood-pressure is that published by Kolls (1). Apart from the difficulty of following rapid changes of blood-pressure by means of his electro-magnetic valve, the maximum safe duration of an observation is at the most ten minutes, as it involves the complete occlusion of the main artery of supply to the limb, and frequent repetition has been known to cause the appearance of ecchymoses in the extremity. A method for recording changes in blood-pressure has recently been published by Thompson (2), consisting of a modified water manometer connected to a special armlet. The method records variations in blood-pressure and not the systolic pressure, but Thompson points out that the latter can be arrived at by calculation. We had discarded a similar method in the course of our investigations, since we found that any changes in the soft tissues on which the armlet presses, such as alterations in muscle tonus of which the subject may be quite unaware, introduced an error of considerable magnitude, and one which it is exceedingly difficult to detect. In the tracing, an increase of tonus is translated as a rise, and a decrease of tonus as a fall of blood-pressure. The slow and gradual nature of such tonus changes renders them particularly liable to such misinterpretation. The constantly occurring variations of the skeletal muscle tonus in their relation to cerebral activity have been somewhat exhaustively studied by us in some already published work (3, 4). Any slight physical or psychical disturbance will be accompanied by a rise of tonus that demonstrably affects the pressure of a balloon contained in the cuff encircling the limb.

[1] Received August 12, 1929.

The following appear to be the conditions which must be fulfilled in the continuous recording of systolic blood-pressure in the human subject. An oscillometric method is the most suitable, involving a transmitting capsule inflated at a pressure well below the systolic blood-pressure. The capsule should be applied to a single artery, and the artery chosen should possess a very free anastomosis both above and below the compressed area. There should be an absence of important veins in the region subjected to pressure. The artery should be supported by bone, with a minimum of soft tissues, particularly muscle, over and around it. The pressure bag should be applied to the limb in such a way that it is supported by bony and ligamentous structures only, no pressure being brought to bear on soft tissues whose resistance is variable. It is important that the cuff, when applied and fully inflated, should cause no discomfort to the subject. Lastly, the recording apparatus must be such as to give a true reading for any pressure of the transmitting bag.

Method.

The artery chosen by us is the dorsalis pedis, just below the anterior annular ligament, where it may be seen or felt pulsating. It lies on the unyielding bed formed by the tarsal bones and the intervening ligaments. The anastomosis of the dorsalis pedis with the external plantar, the external malleolar and peroneal arteries is so free that its complete occlusion at this point would cause practically no disturbance. The small veins in this region form part of a freely anastomosing network, and can also be interrupted with impunity.

The pressure bag applied over this area of the artery is a round rubber capsule of about $2\frac{1}{2}$ inches diameter contained in a net, by means of which it is sewn to the under-surface of a firm band of strapping 4 inches wide. Expansion of the rubber capsule can only take place away from the strapping, the net preventing its being inflated beyond a certain safe limit. The strap is applied across the ankle-joint, and each corner of it is provided with a tape. The two upper tapes are tied over the posterior surface of the os calcis at the insertion of the tendo Achilles, while the lower two wind round either side of the foot and are tied under the anterior end of the os calcis, being supported by the plantar fascia and ligaments. The band thus firmly fixes the capsule in position without pressing on yielding muscular tissues.

The recording of the pulsations imparted to the pressure capsule by the artery is effected by the ingenious sphygmographic tambour of Pachon. This is so arranged that the pressure obtaining in the capsule is distributed not only within, but also without the recording tambour, the latter being contained in an enveloping box which is in direct communication with the pressure system. The instrument thus remains equally sensitive at any degree of pressure. As in the well-known Pachon oscillograph, the size of the oscillations is used as an index in the evaluation of the actual blood-pressure. Thus the mean pressure is given by the manometer reading of the applied pressure when the oscillations

are at their maximum, and the systolic pressure by the reading taken when the first definite increase of pulsations occurs. The accuracy of the method was tested by comparing the systolic pressure readings obtained in the arm by the conventional Riva Rocci apparatus with the oscillographs from the dorsalis pedis. In the sitting position the difference between the two measurements was exactly proportional to the difference in level of the two limbs, and the difference disappeared when the arm measurements were repeated in the supine position.

We found it convenient to photograph the reflection from a light mirror attached to the tambour instead of using the usual mechanical lever, thus obtaining a greater magnification than is possible with smoked paper records. With a fair degree of magnification, the preliminary calibration allows of an easy determination of the systolic and mean blood-pressure to two millimetres of mercury (Pl. 10, Fig. 1). Once this determination has been made, the pressure is set at a point above the mean pressure and below the systolic, and the record is taken without further adjustment.

The method under consideration seems to fulfil the requirements enumerated in all essentials. The error introduced by alterations of muscle tonus is eliminated by not allowing the cuff to rest on muscle tissues, but it is still possible by movement of the ankle and tarsal joints to introduce irregularities into the record. Such movements can be reduced to a minimum by adequately supporting the limb in a comfortable position, and we use a back splint with an adjustable hinge, which rests firmly on a couch, and to which the leg and foot are bandaged in the required position. By means of this it is quite easy to obtain readings extending over long periods without the occurrence of the slightest movement. The greatest safeguard against errors introduced by movement, however, is the fact that the records give unmistakable evidence of it, even if it is so slight that the subject remains unaware of having moved.

A rise of systolic blood-pressure will be represented by an increase in the size of the oscillations, and with the help of the preliminary calibration the degree of that rise can be numerically determined. The selection of the pressure at which the record is to be taken must be based on considerations as to the probable magnitude and direction of the change in systolic pressure that will result under any given experimental conditions. Where these are such that the relatively small variations of pressure in either direction are to be expected, the pressure-point of choice will be one about midway between the systolic and mean pressures. If, however, a considerable rise of blood-pressure be anticipated, the pressure will obviously have to be adjusted as near as possible to the mean point ; while in the reverse case, i. e. where a considerable fall is expected, the point selected will still be below, but as near as possible to the systolic pressure. These considerations, however, practically only apply to the study of the action of drugs causing very drastic changes in blood-pressure. For the correct interpretation of small variations in blood-pressure it is important to remember that fluctuations of blood-pressure are constantly occurring which are dependent on the respiratory rhythm. Their effect is eliminated by measuring

and comparing pulsations occurring during any one given phase of respiration only. Whilst the difference between the expiratory and inspiratory blood-pressures during normal breathing only amounts to about 2–3 millimetres, it can easily reach 10–15 millimetres during deep breathing (Pl. 10, Fig. 2).

A study of the records obtained by the method under consideration has brought to light many hitherto unsuspected concomitants and after-effects to well-known blood-pressure reactions. Thus the rise of pressure occasioned by a painful stimulus is at its inception accompanied by the familiar tachycardia, and is followed on cessation of the stimulus by a slowing of the heart beat and an exaggeration of the normal expiratory slowing. This alteration of the cardiac rhythm persists till the blood-pressure has again reached normal limits (Pl. 10, Fig. 3).

The fall of blood-pressure and concomitant tachycardia caused by the administration of amyl nitrite was followed by a well-marked rise of pressure, accompanied by some slowing of the heart-beat; this rise was found in some subjects to last for more than twice the period occupied by the original fall (Pl. 10, Fig. 4).

The fact that observations can be taken over long periods without the subject being aware of, or inconvenienced by, the apparatus has enabled us to obtain continuous records during sleep, anaesthesia, hypnosis, and over long periods of intellectual work. These investigations are not yet complete, and their results will be published elsewhere. In the meantime, the method having proved of such general clinical applicability, it was decided to bring it to the notice of physicians in the above preliminary note.

We wish to thank the Medical Research Council for a grant which has enabled one of us to undertake collaboration in this piece of work.

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DESCRIPTION OF PLATE.

FIG. 1. Calibration curve. To be read from left to right. Initial pressure 130 mm. Hg, descending by steps of 10 to 40 mm. Hg. Systolic pressure between 130 and 120 mm.; mean pressure 70 mm. Hg.

FIG. 2. Record showing the influence of respiration on blood-pressure. Upper line pneumographic curve of respiration—upward movement inspiration, downward expiration. Lower line oscillogram. Normal breathing to left of dark line, deep breathing to right. Inspiratory blood-pressure about 10 mm. Hg lower than expiratory during deep breathing.

FIG. 3. Effect of pain on blood-pressure. Pain stimulus applied to ear between two vertical dark lines. Rise of B.-P. about 15 mm. Hg with tachycardia. Followed by slowing of heart-beat on cessation of stimulus. Lower line time in minutes.

FIG. 4. Effect of inhalation of amyl nitrate for $\frac{1}{2}$ minute. Inhalation begins at vertical dark line (read left to right). B.-P. falls from 115 mm. Hg to 80 mm. Note tachycardia. Subsequent rise to 135 mm. Hg with slowing of heart. Lower line time in minutes.
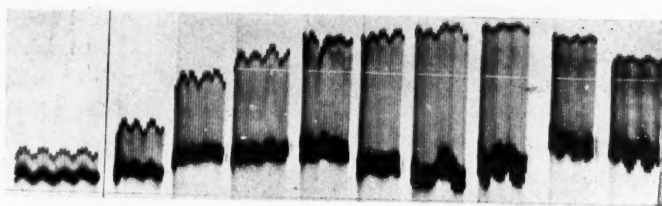
Fig. 1
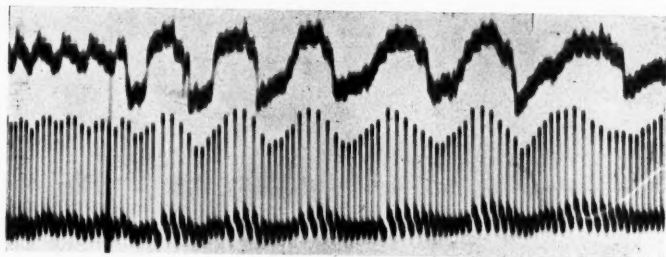
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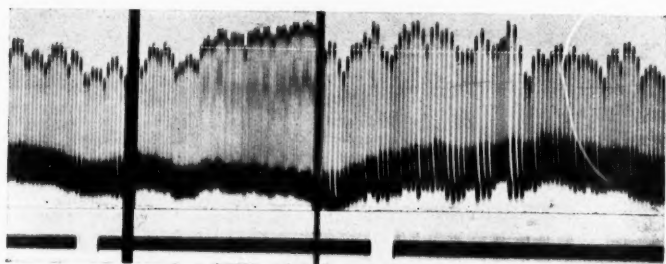
Fig. 3
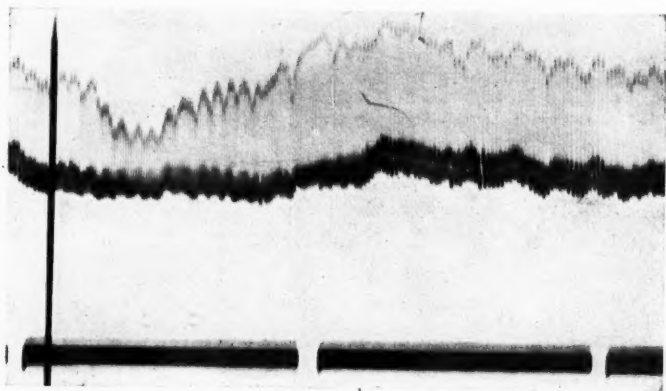
Fig. 4

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ALKALAEMIA IN THE DIARRHOEA OF INFANTS[1]

By MONTAGUE MAIZELS and CATHERINE B. McARTHUR

(From the Department of Pathology, The Infants Hospital, Westminster)

HARTMANN AND SMYTH (1) have described a series of cases in which vomiting had resulted in excessive loss of acids and salts. In some of these cases, although alkalaemia was present, the urine was acid in reaction. The present writers (2) have also noted this occurrence in certain cases of diarrhoea in infants. Hartmann and Smyth attribute the phenomenon to retention of base by the kidney, depending upon the lowered osmotic pressure of the blood, depleted of its salts. As, however, in cases of vomiting with alkalaemia, it sometimes happens that the urine is acid when the osmotic pressure of the blood is normal, and alkaline when the osmotic pressure is low, other factors must be considered in addition to variations in the osmotic pressure of the plasma. Thus it is possible that the retention may be due, in some cases, to an altered threshold for base consequent upon renal damage, and that the changes in the blood are secondary to deficient excretion by the kidney such as was described by Henderson and Palmer (3) in nephritis. It is in support of such a possibility that the cases in the accompanying table are described.

Table I illustrates cases of diarrhoea and vomiting in which renal damage is almost certainly present, and in which base retention occurs, although the osmotic pressure of the plasma is normal or raised. Only Cases 2, 3, and 4 had received treatment with alkali before the blood examinations were made.

It will be seen that the pH of the blood is increased (normal, 7·31–7·40), that the plasma bicarbonate is raised (normal, 0·022–0·028 molar), and that the plasma chloride is also raised (normal, 0·096–0·106 molar).

The urine is acid. Acidity is specially marked in Cases 1, 2, 3, and 4. The titratable acid exceeds the ammonia combined acid. The ammonia coefficient is usually low.

That renal function is impaired is made probable from the following observations :—First the plasma phosphate was estimated in three cases (2, 5, and 6) and found to be raised. Secondly, the titratable acid is greater than the ammonia combined acid. This indicates that the ammonia content of the urine is relatively low and that much of the acid is combined not with ammonia but with fixed base. Such a relative deficiency is probably due

TABLE I.

Case No.	Date	Remarks	Motions	Vomits	Blood pH	Plasma Bi-carb. Molar.	Plasma Cl. Molar.	Urine pH	Titratable Acid.	NH₃ Combined	Ratio	Urea	NH₃ coefficient	Chlorides	Phosphates	Acetone Bodies
1	26.3	G. N. 6 lb. 9 weeks. 3 days' history. Dehydrated.	7	5	—	0·033	0·110	5·2	102	50	0·49	2·3	6·0	0·26	0·14	0
	2.4	Worse. Died 4.4	5	—	—	0·034	0·102	6·6	11	17	1·54	0·82	5·7	0·03	0·44	—
2	24.6	S. C. 7 lb. 9 weeks. 2 weeks' history. Dehydrated. Has had alkali by mouth. Plasma P. = 8·7 mg.	10	5	7·39	0·033	0·116	5·0	96	66	0·69	1·81	10·2	0	0·10	0
	25.6	Died on 27th	—	—	—	—	—	5·0	92	52	0·56	1·5	9·7	0·1	0·13	0
3	15.7	R. W. 8 weeks. Marasmus. Mild D. and V. for several weeks	5	1	7·53	0·046	0·113	5·4	62	40	0·65	3·85	2·9	0·07	—	—
4	15.7	J. G. 8 lb. 6 weeks. 2 weeks' history. Dehydrated	6	8	7·3	0·009	0·117	5·0	80	92	1·14	3·6	7·2	0·07	—	0
	17.7	Given alkali by mouth. Died 21.7	6	6	—	0·031	0·107	5·0	58	55	0·95	2·02	7·6	0·57	0·40	0
5	8.7	R. B. 7 lb. 6 weeks. D. and V. since birth	9	9	7·4	0·022	0·107	5·2	85	46	0·54	4·15	3·1	0·06	0·61	0
	10.7	Very dehydrated. Comatose. Plasma P. = 10·2 mg.	9	4	7·5	0·040	0·118	—	—	—	—	—	—	—	—	0
	11.7	Had glucose 5 per cent., subcutaneous 4 oz. Water by mouth. No dehydration. Marked cerebral irritation.	5	2	7·45	0·081	0·117	6·3	20	14	0·70	3·35	1·2	0·31	0·05	0
	12.7	Died on 18.7	10	12	7·48	0·035	—	—	—	—	—	—	—	—	—	—
6	18.7	J. C. 7 lb. 6 weeks. Diarrhoea 10 days. Plasma P. = 8·0 mg.	6	6	—	0·028	0·103	6·8	10	6	0·60	0·64	2·6	—	—	—
	26.7	Dehydrated. Semicomatose. Plasma P. = 11·4 mg. Died 27.7	14	5	—	0·033	0·114	5·6	72	16	0·22	3·6	1·2	0·02	0·56	0
7	29.7	S. A. 12 lb. 9 months. 3 days' history. Dehydrated. Improved. Has had oral and subcutaneous glucose, and insulin, 3 units, daily	3	6	7·44	0·035	0·102	5·8	64	44	0·68	2·3	5·3	0·03	0·13	+++
	31.7		—	8	—	0·023	0·092	6·2	34	110	3·2	3·1	10	0	0·10	++

to the inability of the kidney to form ammonia. This sign of renal failure is especially prominent in Case 6.

It is interesting to note that this deficiency in urinary ammonia sometimes occurs in cases of diarrhoea with alkalaemia in which the osmotic pressure of the plasma is less than normal (2). In such cases, lowered osmotic pressure, on the one hand, creates a need for retention of base by the kidney, while on the other, deficient ammonia formation necessitates the excretion of fixed base to combine with the urinary acids. The chemical findings in such cases, will be the resultant of these opposing factors.

It will be seen that the kidneys are still able to excrete considerable quantities of fixed base, in spite of the raised threshold.

The chloride content of the urine is variable. It is sometimes very low, even when the plasma bicarbonate and chloride are raised. (Cases 1 (2 IV); 2 (24 VI); 3; 6 (26 VII); and 7). This suggests deficient excretion.

It will be noted that the phosphate content of the urine in Cases 1 (28 III); 2 (24 VI); and 7 (29 VII) is much less than would have been expected from the titratable acidity. Presumably, in such cases other weak acids must be present besides phosphoric; diacetic acid in Case 7, but not in the other cases.

Casts were not found in the urines, but traces of albumin were often present.

TABLE II. *The Chloride Content of the Red Cells.*

No.	Plasma bicarb.	Plasma Cl. molar.	Cell Cl. molar.	Ratio.
1	0·033	0·110	0·051	2·15
2	0·031	0·116	0·053	2·20
3	0·046	0·113	0·048	2·35
4	0·031	0·104	0·032	3·25
5	0·031	0·117	0·035	3·33
6	0·033	0·114	0·047	2·43
7	0·035	0·103	0·045	2·30
Normals Average 15	0·025	0·103	0·053	1·94

(Range: 1·76–2·17)

The ratio of plasma chloride to red cell chloride is increased; the cell chloride being normal or less than normal. This finding is usually present in cases of diarrhoea and in cases of vomiting with alkalaemia (e.g. pyloric stenosis), whatever the chloride content of the plasma may be, so that when the plasma chloride is normal, the cell chloride may be far below normal, and even when the plasma chloride is greatly lowered, the reduction of cell chloride may be still more marked.

The methods used in this investigation are the same as those mentioned in a previous communication (2), except that phenolphthalein was used as the indicator in titrating the urine.

The separation of cells and plasma for chloride estimation was accomplished by centrifuging the blood in a tube four millimetres wide at four thousand revolutions a minute for twenty minutes. Errors arising from residual plasma among the red cells are quite small and fairly constant.

Conclusions.

1. Cases of diarrhoea in infants are described, in which the blood is more alkaline than normal, and in which the osmotic pressure of the plasma is increased, yet the reaction of the urine remains acid.

2. It is thought that this occurrence is due to deficient excretion of base consequent upon renal damage.

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THE ORIGIN AND OCCURRENCE OF LACTIC ACID IN HUMAN GASTRIC CONTENTS WITH SPECIAL REFERENCE TO MALIGNANT AND NON-MALIGNANT CONDITIONS[1]

By E. C. DODDS and J. D. ROBERTSON

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Historical.

FROM the time when test-meals in one form or another were first performed workers have sought, and have often claimed to have found, specific changes in the composition of the gastric contents in carcinoma ventriculi. From the chemical point of view two important claims have been put forward, namely, the absence of hydrochloric acid and the presence of lactic acid.

A great many papers have appeared on the former question, and a considerable amount of careful and accurate quantitive work has been done, though the earlier publications are really of little value when the type of test-meal employed is considered. The modification of the Ewald test that was used extensively before the war seldom included the essential act of emptying or washing out the stomach before the test-meal was given, and consequently the findings with regard to the presence or absence of hydrochloric acid after one hour is of little value.

The introduction of the fractional test-meal in 1914 by Rehfuss (1) resulted in a revision of opinion with regard to the diagnostic importance of the absence of hydrochloric acid, and the method enabled certain difficulties to be overcome. Thus, the stomach is emptied prior to the test, and in all cases of doubt is washed out with water to ensure that the interior is free from residual material. As has been pointed out by many workers, this has demonstrated that in a large percentage of cases the achlorhydria occurring in carcinoma of the stomach, and particularly in the early stages of this condition, is apparent and not real. Bennett (2) proved that a secretion of hydrochloric acid could be evoked in many cases of apparent achlorhydria if precautions were taken to wash the stomach clean, and Rehfuss (3) states that if care is taken to ensure that the stomach is clean, free hydrochloric acid may be demonstrated in one half of the cases of carcinoma. The view has developed that achlorhydria in carcinoma of the stomach is often due, not to specific inhibition or neutralization, but to the fact that the interior of the organ becomes filled with products of retention and

[1] Received September 27, 1929.

foul debris, with the result that the mucous membrane becomes so coated over that the normal stimulus for food cannot reach it; by washing out the stomach and cleaning the walls, secretion can usually be evoked. The recent work with histamine (4) indicates that the secretion of hydrochloric acid can practically always be induced in the stomach by the use of this agent, and it is safe to say that consensus of opinion is levelled against the view that the absence of hydrochloric acid is an essential finding in cases of carcinoma of the stomach.

If we turn to the second claim, namely, the presence of lactic acid as an invariable sign of gastric carcinoma, it is soon apparent that the problem cannot be answered from a study of the literature. The presence of lactic acid in gastric contents has received attention for a great number of years. Following the discovery of hydrochloric acid in the stomach by Prout (5) in 1824, controversy arose as to whether hydrochloric acid was the only acid present in the gastric juice. This was considered to be settled by Schmidt (6) some thirty years later when, after a very prolonged series of analyses, he found that only hydrochloric acid was present in the resting gastric juice, but that later specimens, removed during the course of digestion, frequently contained lactic acid. It was assumed that the lactic acid present in these later specimens was due either to the substance being introduced with the food, or through fermentation of carbohydrates. Then a later view gained a great deal of support from the experiments carried out upon the digestion of herbivorous animals, whose stomachs were found to contain considerable quantities of lactic acid (7). Following this, the work of Prout was contested by many physiologists, who maintained that the acid of the gastric contents was lactic acid, and from 1840 onwards a long and bitter controversy was waged concerning the acid of the stomach. As already mentioned, the work of Schmidt in 1852 settled the problem of hydrochloric acid finally. From this date it was agreed that this was the chief acid of the gastric juice, but that lactic acid often occurred, particularly during the course of gastric digestion.

The position has been summarized in papers by Ewald and Boas in 1885 (8), and again in Ewald's book in 1890 (9). These observers considered lactic acid to be present normally in the stomach during the course of digestion, and held that it was produced rapidly by the action of enzymes and bacteria on carbohydrates, but that in the normal stomach it was absorbed and therefore frequently escaped detection. It might, however, be detected very early in the course of a test-meal. In later papers, Boas (10) came to the conclusion that the appearance of lactic acid in the gastric contents could be regarded as a specific sign of carcinoma. He maintained that it appeared at a very early stage of the disease, and was more or less independent of the size and extent of the growth and whether gastric retention was present. He estimated the lactic acid quantitatively in many cases. This view was vigorously attacked by Ekehorn (11), Hammerschlag (12), Strauss (13), and others, and it is interesting to note that in a later paper Boas (14) came to the conclusion that the lactic acid production was due to gastric retention and lowered activity, factors which,

of course, could be present in other conditions. As von Noorden (15) says, 'the cause must exclusively be looked for in the combination of impaired motility and a deficiency of HCl'.

Whilst the workers who believe that lactic acid is present in the early stages of the disease do not state in so many words the fact that they thought lactic acid was secreted by the gastric mucosa or growth, a careful study of the papers indicates that this was their view. Later on, the fermentation theory of its origin arose, and this in the main is accepted to-day. There are, however, those who either state or imply that the lactic acid is produced either by the stomach or by the tumour. Thus Craven Moore and Roberts (16) maintain that lactic acid is produced by the tumour, and other writers who maintain that the presence of lactic acid is pathognomonic of cancer, imply that it is secreted by the stomach. One of the main objections to the fermentation theory is the rapidity of the production of lactic acid, but as will be seen later, this is not necessarily an insuperable point.

One of the best ways of settling the problem would be to isolate the lactic acid and determine whether it was laevo-rotary, i. e. sarco-lactic acid, or whether it was inactive, in which case the fermentation origin would be more or less proved. The first attempt to settle this important problem was made by Maly (17) in 1874, but study of his paper shows that his results are not conclusive. He extracted pig stomach mucous membrane obtained from the slaughter-house, and proved that the lactic acid present was the inactive form. He isolated it in the form of zinc salt, and examined it for its rotatory power, water of crystallization, &c. It is, however, difficult to apply his observations direct to the study of the problem in human beings, and we must regard the matter as being still in an unsettled condition. The present writers have been able to examine a case which showed unusually large quantities of lactic acid in the gastric contents, and, as will be described later, the acid was proved conclusively to be optically inactive and therefore almost certainly of fermentative origin.

Some recent writers have tended to revert to the views of Boas, and amongst these may be mentioned MacLean, Craven Moore and Roberts. MacLean (18) stresses the importance of finding achlorhydria and lactic acid in a test-meal, and implies that these are very strong evidence of gastric cancer. Whilst there can be no doubt that these findings should arouse the physician's suspicions, the foregoing study of the literature would indicate that they are far from pathognomonic signs. As will be seen later, any study based on qualitative reactions for lactic acid is subject to criticism.

Craven Moore and Roberts go so far as to state that the presence of lactic acid is pathognomonic of malignant disease of the stomach, and that 'it probably arises by the specific activity of the cancer cells on glucose in the tissue fluids'. It would appear that they regard the presence of lactic acid as evidence of that peculiar type of metabolism of malignant cells described by Warburg (19) and his collaborators. It is difficult, however, to see how lactic acid produced in

this manner could enter the stomach lumen when the disease is in its very early stages. Again, unfortunately, there is no account of any quantitative work having been performed.

Present Investigation.

Realizing that the whole problem warranted very careful analytical investigation, and a large amount of clinical material being available, the test-meals were performed on the patients by the authors themselves in the Courtauld Institute of Biochemistry, and it was thus possible to control all essential details, such as washing out the stomach, uniformity in the preparation of the test-meal, and so on. It was decided to employ the tests recommended by MacLean, but in addition the lactic acid was estimated quantitatively in the resting juice and in one or more of the subsequent specimens removed during the course of the test-meal. By this means it became possible to compare the value of the qualitative tests for lactic acid with a quantitative method of proved accuracy.

The investigation consisted in performing test-meals on 73 consecutive cases presenting themselves at the Institute for fractional test-meal examination. The patients were derived from the medical and surgical departments of the hospital, and the examinations were undertaken at the request of the physicians and surgeons in the course of the routine examination of the patients. The special study lay in an examination of the various specimens for the presence of lactic acid by both qualitative and quantitative tests.

Technique.

1. *The Test-Meal.* The fractional method of gastric analysis is described by Rehfuss was employed. The actual technique used being essentially the standard procedure, of which an account may be found in Bennett's work (20). Especial care was taken in the collection of the resting juice and in the emptying of the stomach. When the resting juice had been removed, the stomach was washed out very carefully, in every case with a large volume of water, until the washings were clear. The test-meal itself consisted of oatmeal gruel, always prepared in the same way. A careful series of preliminary experiments proved that there was no lactic acid present in this substance.

2. *Examination for the Presence of Lactic Acid.* Two series of tests were employed, (*a*) qualitative, and (*b*) quantitative. It was found impossible to perform all these tests upon every specimen removed during the course of gastric analysis, both from the point of view of the labour involved, and also owing to the fact that there would not have been sufficient material in every specimen. It was finally decided to perform the qualitative and quantitative tests upon (1) the resting juice, and upon (2) the pooled specimens of the later

fractions removed in each case. The specimens were filtered through Schleicher and Schüll filter-paper prior to the examination.

(a) *Qualitative Tests.* Two reactions were employed; a modified ferric chloride reaction in which a solution of ferric chloride and mercuric chloride were added to the gastric contents in the manner described by MacLean (18; p. 125) and MacLean's modification of the Hopkin's thiophene test (18; pp. 125–6). The technique of MacLean was strictly adhered to.

Before applying these reactions to our series of cases, their sensitivity was tested experimentally. There was no difficulty in confirming that the ferric chloride and thiophene tests will detect concentrations of lactic acid down to 0·005 grammes per cent. when the lactic acid is in simple aqueous solution. If, however, the test be repeated with lactic acid dissolved in the oatmeal gruel test-meal, the sensitivity at once falls off, and it is only possible to detect concentrations of lactic acid down to 0·02 per cent. It is, however, necessary in our opinion to perform a third preliminary test, namely, to investigate the sensitivity of the reaction when the lactic acid is added to actual gastric contents, i. e. material removed from the stomach by a tube.

To investigate this problem, the lactic acid was added to material removed from a stomach after administration of the usual test-meal, and which was found by quantitative analysis to contain no lactic acid. Difficulties were encountered at once. It was found, for instance, that if there was any trace of bile or its derivatives present in the contents, the ferric chloride and thiophene test became so obscured as to be worthless; this was because the ferric chloride reaction showed a precipitate in the presence of bile which rendered the interpretation of the results very difficult, in addition to being obscured by the colour of any bile pigments present. The effect on the modified thiophene reaction was still more serious. A long series of experiments showed that it was very rare indeed to obtain either a clear-cut negative or a clear-cut positive with this reaction ; either one or both of two events occur. On the addition to sulphuric acid in the later stages of the test, a brown colour appears, due possibly to charring. This completely obscures any cherry pink colour that may follow on completion of the test. It was found that many of the gastric contents giving this reaction also reduced Benedict's solution, and it appeared that the charring in some cases was due to the production of a readily charring and reducing carbohydrate from the starch of the gruel, probably by the action of ptyalin.

A second difficulty noticed during the performance of a series of this modified reaction was the appearance of a green fluorescence after the addition to the sulphuric acid. This was particularly marked if the specimens contained bile, and occurred also when no pigment could be detected by inspection. It was found that similar results could be obtained if a solution of bile salts was added to an aqueous solution of lactic acid prior to performing the thiophene reaction, and it is suggested that this fluorescence is due to the presence of bile salts or cholesterol in the stomach, which may be present even when pigments cannot be detected with the naked eye. These two reactions, namely, the ferric

chloride and thiophene tests, have been found to be most unreliable and mis-leading when compared with the quantitative estimations of lactic acid in the specimens.

It is interesting at this point to digress for a moment and consider the suggestion made by MacLean (18, p. 100) that many cases of cancer of the stomach showing free hydrochloric acid are the result of chemical mistakes, and that the 'large amount of hydrochloric acid was really a large amount of *lactic acid*'. Investigations in which lactic acid was added to the oatmeal gruel in sufficient quantity to give a positive reaction with Toepfer's reagent demon-strated that the concentration of acid had to reach 3·6 per cent. If the gruel was filtered, a faint pink could be detected in 1·8 per cent. Similar results were obtained using the contents withdrawn from a fasting stomach in place of oatmeal. It will be seen that these concentrations are much greater than the highest concentration of lactic acid discovered in our series. It seems unlikely, therefore, that MacLean's argument has justification.

(b) *Quantitative Tests.* The estimation of lactic acid, even in aqueous solution, presents many difficulties, and in order to solve this problem it is necessary to consider, firstly, a method for the extraction of lactic acid from the gastric contents in order to avoid the action of various interfering substances, and, secondly, to employ an accurate method for the estimation of the acid so extracted. Friedemann, Cotonio, and Shaffer's (21) modification of Clausen's (22) technique has been used in this department for some considerable time, and careful study of the accuracy of the method has been made. Thus Baker, Dickens, and Gallimore (23) have shown that '33 estimations on a solution of pure zinc lactate gave a mean recovery value of 99·4 per cent., the extremes being 104 per cent. and 94 per cent'. The apparatus used for the determination is described in the paper referred to (21), but a few minor alterations were made. Thus, in view of the small quantities of lactic acid present in the gastric contents, it was found advantageous to use outside air for the aspiration, and to reduce the size of the receivers. Centrifuge tubes of 50 c.c. capacity were found to be the most convenient. By this modification the yield of bisulphite-binding substances other than lactic acid was reduced to a minimum. A long series of experiments was performed in order to determine the best method of extracting lactic acid from gastric contents. The method finally arrived at consisted in adding plaster-of-Paris to the contents in sufficient quantities to make the mixture set solid, and after this has been broken up, the lactic acid is extracted with ether in a Soxhlet apparatus. The final method devised is as follows :

Two c.c. of filtered gastric contents are taken, and 2 drops of 50 per cent. sulphuric acid added. This is followed by the addition of enough plaster-of-Paris to make the mixture set to a solid mass, 3 gms. being about the quantity required. After breaking up to a number of small pieces, the plaster-of-Paris is carefully transferred to an extraction thimble, and the lactic acid is extracted with ether in a Soxhlet apparatus for 1½ hours. At the end of this period the

Soxhlet apparatus is removed and 10 c.c. of water added to the flask containing the ether. One drop of phenolphthalein solution and enough N/10 NaOH to make the water just alkaline are added and the whole shaken round vigorously. The ether is then evaporated off and the aqueous layer evaporated to dryness. The residue is then dissolved in 50 c.c. water, and the ordinary lactic acid method referred to above is proceeded with. It has been necessary to determine blank values on the ether used, and a series of these determinations showed that small and consistent blanks are obtained, namely, about 0·4 c.c. N/500 iodine.

Test of the Method. The length of time of extraction of the plaster-of-Paris was controlled by extracting 20 mg. of lactic acid from a plaster-of-Paris mixture. At the end of every half-hour the extraction was interrupted and the ether extract was removed. The lactic acid content of this was determined, and the extraction was continued with a fresh supply of ether. The following table shows that 99 per cent. of the lactic acid was extracted in 1½ hours.

TABLE I.   *Rate of Extraction of Lactic Acid from Plaster-of-Paris.*

Solution of 20 mg. of Lactic Acid Dehydrated with Plaster and Extracted.

Time of Extraction.	Lactic Acid Extracted.	
Minutes.	grm	%.
30	1·50	75
60	0·34	92
90	0·14	99

The limits of sensitivity of the method have been investigated by taking gastric contents known to contain no lactic acid and adding varying quantities of pure lactic acid in order to give a range of concentrations. The estimation was then proceeded with in the manner described. Table II shows the actual quantities of lactic acid added, together with the amount found experimentally. The percentage recovery is also shown.

TABLE II.   *Added Lactic Acid Recovered from Unfiltered Gastric Juice*

Lactic Acid Added per 100 c.c. Gastric Juice.	Lactic Acid Recovered per 100 c.c. Gastric Juice.	
grm.	grm.	%.
0·0058	0·0050	86
0·0180	0·0151	83
0·0610	0·0520	86
0·0610	0·0520	86
0·0610	0·0590	95
0·0610	0·0550	90
0·0610	0·0639	105

An examination of these results shows that the method is surprisingly accurate, and even in such small concentrations as 0·001 per cent. the accuracy is of a sufficiently high standard to be a definite statement as to whether lactic acid is present or not.

TABLE III. *Added Lactic Acid Recovered from Oatmeal Gruel.*

Lactic Acid Added per 100 c.c. Oatmeal.	Lactic Acid Recovered per 100 c.c. Oatmeal.	
grm.	grm.	%.
0·0013	0·0015	115
0·0013	0·0016	123
0·0026	0·0025	96
0·0039	0·0034	87
0·0052	0·0047	90
0·0064	0·0063	98
0·0160	0·0178	111
0·0910	0·0920	101
0·3900	0·3700	95
0·8900	0·9000	101

Isolation and Investigation of Lactic Acid from Gastric Contents.

As already pointed out, the desirability of isolating lactic acid and examining it in order to determine whether it is sarco or fermentation lactic acid is very important. The great difficulty in the way of such an investigation lies in the small amount of lactic acid present in gastric juice, even in cases of fairly advanced carcinoma. It is only very exceptionally that a high lactic acid content is found, and the fact that this investigation has not been performed is sufficient testimony to the rarity of suitable cases. The following patient, however, proved to be suitable for such an investigation.

We have to thank Dr. G. E. Beaumont, under whose care the patient was admitted to the Middlesex Hospital, for permission to record his symptoms and for giving us every facility for investigating the case.

The patient, T. H. (No. 69, Table VI), aged 57, was admitted complaining of pallor, shortness of breath, and oedema of the legs, abdominal wall, and arms; the face showed a rather brownish lemon-yellow pigmentation. He gave a past history of illness for some four years without special features; the appetite had diminished during the past seven months. A clinical examination revealed nothing abnormal other than a systolic murmur of the apex, a low blood-pressure—115/57—and the oedema already referred to. The blood-count performed by the Bland-Sutton Institute of Pathology showed a severe secondary anaemia. Examination of the faeces revealed the presence of occult blood, together with a high total fat. Blood analysis showed nothing striking other than a great diminution in the total solids and the absence of bile pigments. A test-meal gave the curve exhibited on p. 183.

Resting Juice. Volume 120 c.c. Much dark-brown sandy debris present, rendering the withdrawal of resting juice slow and tedious. The odour was butyric, but not actually foul. Mucus and bile absent. Starch present and some altered blood.

The stomach was then washed out with water by means of a syringe until the washings were returned clear. This required 900 to 1,000 c.c. water.

The meal was then given by mouth and the contents aspirated every ¼ hour until 1½ hours, when the stomach was empty.

This examination has been repeated on several occasions, and similar results have been obtained. The most noticeable point is the very high total acidity, namely, 155 c.c. N/10 NaOH per cent., of the resting juice associated with
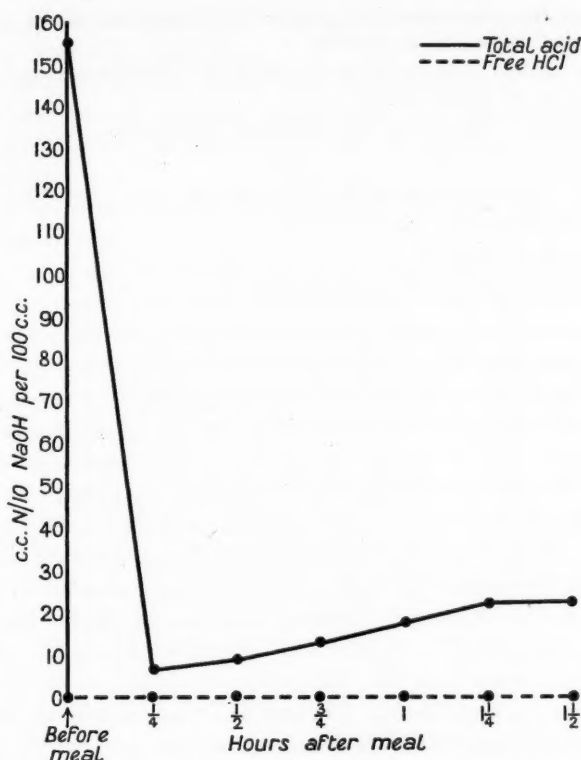
complete absence of free HCl. This immediately led to the suspicion that a large amount of lactic acid was present. The resting juice and each separate specimen were accordingly analysed, with the following result:

TABLE IV.

	R. J.	$\frac{1}{4}$ hr.	$\frac{1}{2}$ hr.	$\frac{3}{4}$ hr.	1 hr.	$1\frac{1}{4}$ hrs.	$1\frac{1}{2}$ hrs.	First Washings 400 c.c.
Lactic acid grm. %	0·825	0·035	0·122	0·032	0·044	0·137	0·244	0·225

It is obvious that this case was peculiarly adapted to the investigation of the nature of lactic acid. The method adopted was that described by Warburg (19), and is very similar to the older techniques mentioned previously.

The patient died shortly afterwards, and an extract of the post-mortem records of the Bland-Sutton Institute of Pathology was as follows:

General. Anaemia. Anasarca. Streptococcal infection of peritoneal effusion.

Heart. Fatty myocardium. Relative incompetence of mitral and tricuspid valves.

Trachea and Lungs. Contained inhaled stomach content. Oedema.

Liver. Small. Veins dilated. Free iron present in small amount.

Stomach. Large fungating growth involving 2/3 of stomach surface, ceasing abruptly at pylorus and invading cardiac end irregularly.

Lymphatic Glands. Glands of greater and lesser curvatures and lumbar glands infiltrated by fine white growth.

Kidneys. Slight narrowing of cortex, with a certain amount of fibrosis, otherwise no marked abnormality.

Bone Marrow. Marrow of long bones red throughout.

Sections :

Stomach. Tubular columnar-celled carcinoma.

Gland. Invasion by similar growth.

Kidney. Early fibrosis.

Bone Marrow. Erythroblastic reaction.

The lactic acid is separated as zinc salt in the manner described : 60 c.c. of resting juice (estimated lactic acid content 0·825 grm. per 100 c.c.) were used for the first preparation. 350 c.c. of stomach washings (estimated lactic acid content of 0·225 grm. per 100 c.c.) were used for the second preparation. To the resting juice about 5 volumes of absolute alcohol were added ; this was filtered and the alcohol removed by distillation *in vacuo.* The stomach washings, after filtration, were evaporated down *in vacuo* below 50° C.

The concentrated solutions remaining after evaporation were acidified with sulphuric acid, dehydrated with plaster-of-Paris, and extracted in a Soxhlet apparatus for thirty-six hours with ether. After the addition of 100 c.c. water the ether was removed on a steam bath. The solution was then warmed for three hours on a water bath with lead carbonate, allowed to stand for twelve hours in the ice-box, and filtered. The lead was removed from the filtrate with hydrogen sulphide. Excess of hydrogen sulphide was removed by passing air through the warm solution. The filtrate was warmed for two hours on the water bath until crystals began to form. The solution was then allowed to evaporate at room temperature until there only remained about 2 c.c. of mother liquor. The crystals were filtered on a Büchner funnel and washed with a small amount of cold water; the residue was recrystallized. The mother liquors and washings were again evaporated for a second crop of crystals. The salt was air-dried. 0·405 grm. of air-dried salt were obtained from the resting juice, and from the stomach washings 1·167 grm.

Polarization. A saturated solution of the salt from the stomach washings (2·443 grm. per 100 c.c.) was examined in the polarimeter in a 100 mm. tube. The following readings showed it to be optically inactive :

With Distilled Water.		*With Zinc Lactate Solution.*	
1·26°	1·26°	1·25°	—
1·25°	1·25°	1·25°	1·25°
1·25°	1·25°	1·25°	1·25°
1·25°	1·25°	1·25°	—
1·25°	1·25°		

for the laevo rotatory zinc salt.

$$\alpha \frac{20}{D} = -6.06° \text{ (in 9·08 per cent. solution).}$$

Water of Crystallization. The air-dried salt was dehydrated at 106° C. to constant weight for two hours.

Salt from resting juice: 0·0921 grm. lost 0·0165 grm. or 17·9 per cent.

Salt from stomach washings: 0·2209 grm. lost 0·0401 grm. or 18·1 per cent.

For $(CH_3CH(OH)CO_2)_2Zn . 2H_2O$ water of crystallization = 12·9 per cent. [sarco].

For $(CH_3CH(OH)CO_2)_2Zn . 3H_2O$ water of crystallization = 18·2 per cent. [fermentation].

Ash. Resting juice: 0·0756 grm. gave 0·0251 grm. ash, or 33·2 per cent.

Stomach washings: 0·1808 grm. gave 0·0606 grm. ash, or 33·5 per cent.

For zinc lactate per cent ZnO = 33·4 per. cent.

From these experiments it can be seen that the lactic acid is of the inactive variety, and that its origin must have been fermentative. In order to test this theory and to observe the speed of the production of lactic acid, the following experiment was performed :

A small volume of the resting juice already referred to was added to 400 c.c. of gruel. After thoroughly mixing, a sample was taken out and set aside for analysis. The rest was incubated at 37° C. for thirty-six hours and specimens were removed at frequent intervals. The lactic acid content of each was estimated and the total titratable acidity to phenolphthalein was determined in each case. The results are shown in the following table :

TABLE V

Specimen.	Total Acidity c.c. N/10 %.	Lactic Acid grm. per 100 c.c.
Before incubation	3	0·032
1 hour's incubation	3	0·073
6 ,, ,,	15	0·102
12 ,, ,,	34	0·205
24 ,, ,,	53	0·315
36 ,, ,,	70	0·470

Incubation of some uninfected gruel showed that the lactic acid production in twenty-four hours was negligible ; after forty-eight hours it rose from nothing to 0·007 per cent. of lactic acid.

A bacteriological examination of the original resting juice of the patient referred to was performed by Dr. L. E. H. Whitby, who reported that an organism belonging to the acidophilus group was isolated. Therefore work is in progress on the lactic acid production in gruel by this organism. A preliminary experiment showed that the lactic acid production in a gruel infected with the pure culture of this organism is not so great as in the case of gruel to which a little resting juice, from the patient already referred to, has been added. The following table shows the results of experiments made on gruel to which has been added (A) normal resting juice, (B) a pure culture of the Oppler Boas bacillus. In column C will be found the effect of incubating a mixture of gruel and resting juice after passage through a Berkfeldt filter, German V. Column D shows the result of incubating some gruel to which has been added

a small quantity of gruel from the experiment detailed in Table V.   This can be
regarded as a sub-culture of the original resting juice :

Incubation at 37° C.

Hours.		Nil.	1	6	12	24	36	48	72
Estimation of	A.	0·004	0·004	0·004	—	0·005	0·010	0·013	—
lactic acid	B.	0·0015	0·0065	0·0075	0·0115	0·015	0·025	—	—
grm. %	C.	0·003	0·0035	0·003	—	0·005	0·011	0·012	—
	D.	0·0075	0·011	0·0255	0·0485	0·0717	—	0·1215	0·1805

The experiments show that the production of lactic acid cannot be ascribed
to the tumour since it takes place outside the body and even through a sub-
culture of the original resting juice.   The passage through a Berkfeldt candle
removes lactic acid producing powers, therefore it is safe to conclude that this
is due to an organism.   The fact that the Oppler Boas bacillus produces such
a small quantity of lactic acid is difficult to explain, and it would appear that
the causative organism in this case is some member of the acidophilus group
which cannot be isolated in the ordinary manner.

Results of Test-Meals on Seventy-three Patients.   These results are expressed
in tabular form and include five repeat tests.   The type of test-meal and
examination made has already been described.   The only difficult question is
that of the diagnosis.   The eight cases of carcinoma were diagnosed either by
abdominal section, X-ray, or post-mortem findings.   In the sixty-six non-
malignant cases every care was taken to exclude the possibility of carcinoma of
the stomach.   Many of the patients were adults with vague gastro-intestinal
symptoms, who were sent for a test-meal in the course of their routine
examination.   In the majority the symptoms disappeared under treatment, and
many of them were written to a year after the test and were found to be alive
and often improved.   It follows, therefore, that the diagnoses are as certain as
it is possible to have them, and that malignant disease was excluded in so
far as is possible without a post-mortem examination.

Discussion.

In considering these results, it is essential to stipulate very carefully from
what point of view they are to be examined and interpreted.   The presence or
absence of a certain constituent in pathological conditions is rarely, if ever, an
absolute matter, and the observer is usually dealing with the relative presence
or absence of the substance in question.

It would appear useful to consider the results from two points of view ;
firstly the clinical, as to whether by ordinary qualitative tests or simple reaction
it is possible to state that the presence of lactic acid is a helpful sign in the
diagnosis of carcinoma of the stomach.   The second point of view is purely an
academic one, namely, whether the presence of lactic acid in gastric contents is
pathognomonic of carcinoma of the stomach ; in other words, whether the lactic
acid is produced in some specific manner by the malignant process and is not

found in any other condition whatsoever. It is obvious that it would be possible for the presence of lactic acid to be of great clinical value in the diagnosis of carcinoma, yet its presence might be non-specific from the academic point of view. The results will therefore be reviewed from these two aspects separately.

There is, unfortunately, no difficulty in answering the first. The qualitative tests for lactic acid are so easily influenced by so many substances that no reliance can be placed upon them. This is true when the tests are performed on the resting juice and also on the pooled later specimens. Common interfering substances are constituents of bile and readily charring carbohydrates, and it is quite possible that other substances in addition to these are responsible. Previous publications on this subject have dealt with the one-hour method of examination, whereas the present investigations were performed on the resting juice and specimens obtained during the course of a fractional test-meal, and it might be argued that the interference was confined solely to the fractional test-meal. This, however, hardly seems likely when it is borne in mind that in every case recorded by us the stomach was carefully washed out before the test-meal was given. It would appear, therefore, that no help can be obtained in the diagnosis of carcinoma of the stomach by the use of qualitative tests, and it follows that any consideration of this question from either of the points of view described at the commencement of this discussion must be based on quantitative methods.

A study of the results proves at once that the second point of view, namely, the absolute specificity of the presence of lactic acid in the gastric contents in cases of carcinoma, cannot be upheld. Excluding the repeats, it will be seen that 46 per cent. of the non-malignant cases showed the presence of lactic acid in the resting juice, and 36 per cent. showed it in the later specimens. Whilst the quantity present in cases of carcinoma is greater in a few instances than that obtained in many of the non-malignant cases, yet there is not sufficient difference in the quantities in many of the cases to render even the quantitative reaction of diagnostic value. The theory advanced by Craven Moore and Roberts that the lactic acid was produced by the specific action of cancer cells certainly cannot be supported in view of our results.

The present writers have been particularly fortunate in that they have been able to establish the origin of lactic acid in a case showing large quantities of this substance. The lactic acid was isolated in the form of a zinc salt from the resting juice and other specimens. This was proved by analysis for the zinc oxide content on ignition to be pure zinc lactate and, by observing its rotation, water of crystallization, and solubility, it was proved to be inactive zinc lactate. The methods used in the preparations were such as were known not to give rise to racemization and therefore it can be conclusively stated that in this case at least the lactic acid arose through fermentation. A study of other cases indicates that the origin is similar, but of course it would be unwise to make a general assertion from a detailed study of only one case. It seems, however, on general

grounds to be much more probable that the lactic acid in all cases owes its origin to fermentation. These observations weaken very seriously the probability of the presence of lactic acid ever taking the position of a pathognomonic sign in the diagnosis of carcinoma of the stomach.

To revert to the practical application once more, no hope can be held out that even the laborious quantitative technique as outlined in this paper could render assistance in the diagnosis of carcinoma because the lactic acid is only found in any appreciable quantity in the later stages of this disease. In the early stages there may be no lactic acid present, or the quantity may be similar to that obtained in many non-malignant types of case.

Summary.

1. The qualitative tests for the presence of lactic acid in gastric contents are proved to be so easily obscured by bile and other substances as to be of little value.

2. An adaptation of Friedemann, Cotonio, and Shaffer's quantitative method for the estimation of lactic acid is described, together with a test of the method proving it to be reliable between a range of 0·01 and 0·9 per cent.

3. Application of this method to seventy-three consecutive fractional test-meals proves that the presence of lactic acid cannot be regarded as a diagnostic sign for carcinoma of the stomach. This substance was found to be present in just under half of the non-malignant cases, and was found to be present in small quantities in several of the malignant ones.

4. In one case the lactic acid was isolated as a zinc salt, and chemical analysis together with polarimetric observations proved it to be the inactive compound. Inoculation of gruel with small quantities of the resting juice proved that large quantities of lactic acid were produced in so short a time as six hours. From this it was concluded that lactic acid, in this case at least, arose through fermentation.

5. These observations taken as a whole indicate that little hope can be entertained that even the quantitative estimation of lactic acid can ever be of value in the diagnosis of carcinoma of the stomach.

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TABLE VI.

Case.	Age.	Sex.	Volume c.c	Resting juice.				Other specimens pooled.				Remarks.
				Description.	Total acid c.c. N/10.	Free HCl NaOH %.	Lactic acid grm. per 100 c.c.	Description.	Total acid c.c. N/10.	Free HCl NaOH %.	Lactic acid grm. per 100 c.c.	
1	53	M	130	Mucus+ Starch+ Blood+. Foul odour	60	Nil	0·55	Mucus+	15	Nil	0·028	Inoperable carc. stomach
2	56	F	4	Normal	8	Nil	—	Mucus+	20	Nil	0·018	Migraine—No lesion of stomach
3	37	F	8	Mucus+	4	Nil	—	½ hr. after meal Mucus++	22	Nil	0·020	Visceroptosis—No lesion of stomach
4	67	F	40	Mucus+	10	Nil	0·004	Mucus+	60	40	0·005	No lesion of stomach
5	54	F	30	Mucus+ Bile+	10	Nil	0·003	Mucus+	52	10	Nil	No lesion of stomach
6	67	M	45	Mucus+	64	46	0·020	Mucus+ Bile+	90	72	0·021	Duodenal ulcer
7	56	M	25	Mucus+	8	Nil	0·010	Normal	94	80	0·042	Gastric ulcer
8	34	M	20	Mucus+	20	Nil	0·001	Normal	60	32	Nil	Gastric ulcer
9	46	F	60	Normal	22	4	Nil	Normal	60	35	Nil	Visceroptosis—No lesion of stomach
10	26	F	25	Normal	8	Nil	Nil	Mucus+	18	8	Nil	'Multiple infective arthritis'—No lesion of stomach
11	48	M	40	Mucus+	16	Nil	0·044	Mucus+	15	Nil	0·020	No lesion of stomach
12	39	M	20	Mucus+	18	Nil	0·009	Mucus+	75	55	0·003	Alcoholic gastritis—No lesion of stomach
13	56	M	40	Starch+	15	4	0·001	Normal	12	Nil	0·018	Secondary anaemia
14	46	M	94	Mucus+ Bile+	13	Nil	Nil	Mucus+ Bile+	72	52	0·007	Tabes dorsalis—No lesion of stomach

No.	Age	Sex										Diagnosis
15	45	M	100	Bile+	50	28	0·001	Bile+	36	20	0·001	Duodenal ulcer. Old perforation
16	35	M	330	Starch+	74	53	Nil	Normal	80	63	0·006	Duodenal ulcer
17	27	M	150	Fresh blood. Mucus+	54	36	Nil	Normal	110	100	Nil	Duodenal ulcer
18	51	F	7	Mucus+	20	Nil	Nil	Normal	90	50	Nil	Gastroptosis — No lesion of stomach
19	49	F	25	Mucus+	10	Nil	0·009	Bile+	90	60	Nil	No lesion of stomach
20	49	M	20	Mucus+	20	Nil	0·012	Normal	55	30	0·001	No lesion of stomach
21	55	F	15	Mucus+	28	18	0·011	Normal	70	46	Nil	Duodenal ulcer
22	35	F	30	Starch+	55	25	Nil	Normal	80	55	Nil	No lesion of stomach
23	46	F	20	Fresh blood. Mucus+	70	60	Nil	Mucus+	100	75	Nil	Gastric ulcer
24	61	F	35	Mucus+ Bile+	40	13	Nil	Mucus+	66	35	Nil	Gastric ulcer
25	44	F	50	Blood+	80	60	Nil	Mucus+	66	35	Nil	Chronic appendicitis
26	51	M	40 / 50	Mucus+ Bile+	26 / 15	12 / Nil	0·005 / 0·005	Mucus+ Bile+ / Normal	40 / 34	14 / 17	Nil / 0·004	Gastric ulcer
27	48	M	50 / 70	Mucus+ Bile+ / Bile+	34 / 33	18 / 18	0·005 / Nil	Normal / Normal	75 / 65	55 / 52	Nil / Nil	Gastritis—No lesion of stomach / Gastritis.
28	60	M	35	Bile+ Mucus+	22	Nil	0·007	Bile+	55	15	0·011	Gastric ulcer
29	41	F	45	Bile+	12	Nil	0·010	Normal	20	Nil	0·005	Carc. stomach. Operable
30	51	M	75 / 40	Normal / Mucus+	100 / 9	70 / Nil	0·006 / 0·006	Normal / Normal	75 / 40	55 / 25	0·004 / Nil	Chronic appendicitis / Chronic appendicitis
31	55	F	25	Mucus+	22	Nil	0·004	Normal	75	50	Nil	No lesion of stomach
32	47	M	55	Foul odour. Blood+ Bile+ Mucus+	20	Nil	0·012	Blood+ Bile+ Mucus+	22	Nil	0·047	Inoperable carc. stomach
33	49	F	35	Foul odour. Blood+	8	Nil	0·005	Mucus+	10	Nil	0·010	Inoperable carc. stomach
34	45	F	40	Normal	12	Nil	0·005	Mucus+	30	Nil	Nil	Haemorrhoids—No lesion of stomach

TABLE VI (*continued*).

Case.	Age.	Sex.	Volume c.c.	Resting juice. Description.	Total acid c.c. N/10.	Free HCl NaOH %.	Lactic acid grm. per 100 c.c.	Other specimens pooled. Description.	Total acid c.c. N/10.	Free HCl NaOH %.	Lactic acid grm. per 100 c.c.	Remarks.
35	59	F	8	Mucus+	15	Nil	0·002	Mucus+	50	31	0·006	Visceroptosis—No lesion of stomach
36	47	M	110	Normal	65	50	Nil	Mucus+	95	75	Nil	Gastric ulcer
37	53	M	100	Bile+	8	Nil	Nil	Mucus+	15	Nil	0·001	Carcinoma. lung—No lesion of stomach
38	49	M	20	Normal	20	8	0·002	Normal	80	60	0·003	No lesion of stomach
39	44	M	70	Normal	60	45	0·006	Mucus+ Bile+	80	50	Nil	Gastro-enteritis—No lesion of stomach
			45	Bile+ ·	67	50	Nil	Normal	58	43	Nil	,, ,, ,,—No lesion of stomach
40	55	F	14	Mucus+	40	24	—	Mucus+	82	40	0·002	Visceroptosis—No lesion of stomach
41	59	M	25	Butyric odour. Blood+ Mucus+	25	Nil	—	Mucus+	18	Nil	0·046	Inoperable carc. stomach
42	39	F	15	Mucus+	15	Nil	—	Mucus+	68	42	0·003	Splenic anaemia—No lesion of stomach
43	45	F	85	Mucus+ Bile+	55	36	0·001	Normal	68	48	Nil	Duodenal ulcer
44	27	M	115	Bile+ Blood+	45	20	Nil	Normal	72	50	Nil	Duodenal ulcer
45	49	M	35	Bile+	20	Nil	Nil	Mucus+	50	32	Nil	Gastric ulcer
46	63	M	65	Bile+ Mucus+	45	15	Nil	Mucus+ Bile+	30	12	Nil	Carcinoma colon—No lesion of stomach
47	50	M	140	Bile+	12	Nil	0·003	Bile+	38	22	0·003	Duodenal ulcer — Gastro-enterostomy performed
			90	Bile+ Mucus+	30	Nil	0·008	Bile+	32	5	0·010	,, ,, ,,
48	50	F	25	Unpleasant odour. Mucus+	22	8	—	Bile+	85	75	Nil	Cholecystitis
49	50	M	13	Normal	42	30	—	Normal	60	40	0·005	Gastric ulcer

50	49	M	200	Blood+	45	30	Nil	Normal	55	45	Nil	Gastric ulcer
51	52	M	90	Blood+ Mucus+	15	Nil	Nil	Normal	52	35	Nil	Pulmonary tuberculosis
52	24	F	25	Normal	10	Nil	—	Normal	50	28	Nil	No lesion of stomach
53	41	F	15	Bile+	5	Nil	—	Normal	35	20	Nil	No lesion of stomach
54	50	M	42	Normal	40	30	Nil	Normal	65	50	Nil	Duodenal ulcer
55	22	M	65	Blood+ Mucus+	25	10	Nil	Bile+	80	60	Nil	Gastric ulcer
56	65	M	45	Bile+	20	5	Nil	Bile+	65	55	Nil	Gastric ulcer
57	—	M	70	Normal	65	48	Nil	Normal	75	55	Nil	Juxta-pyloric ulcer
58	67	M	100	Mucus+	5	Nil	Nil	Normal	45	30	Nil	No lesion of stomach
59	35	M	40	Bile+	40	25	Nil	Normal	55	35	Nil	Pyloric ulcer
60	48	M	8	Bile+ Mucus+	16	Nil	—	Bile+	40	25	Nil	Adhesions—No lesion of stomach
61	56	F	35	Bile+	10	Nil	Nil	Mucus+	10	Nil	—	Pernicious anaemia
62	46	F	40	Bile+ Blood+	30	15	Nil	Bile+	55	40	Nil	Gastric ulcer
63	27	F	80	Bile+ Blood+	20	8	Nil	Normal	45	25	Nil	Chronic appendicitis
64	30	M	45	Blood+ Mucus+	35	15	Nil	Normal	80	60	Nil	Duodenal ulcer
65	37	M	25	Normal	5	Nil	Nil	Normal	70	50	Nil	Gastric ulcer
66	37	M	40	Foul odour. Bile+ Blood+	14	Nil	0·020	Mucus+	12	Nil	—	Inoperable carc. stomach
67	43	M	25	Foul odour. Blood+ Starch+	82	Nil	—	Normal	35	Nil	0·059	Inoperable carc. stomach
68	53	F	830	Bile+ Blood+	113	95	0·016	Normal	68	48	0·008	Gastric ulcer
69	57	M	120	Butyric odour. Blood+	155	Nil	0·825	—	—	—	—	Carc. stomach. See text, p. 49
70	55	F	70	Bile+ Mucus+	35	12	0·004	Mucus+	95	85	—	No lesion of stomach
71	29	M	65	Mucus+	60	44	Nil	Normal	46	36	Nil	Normal control
72	26	M	40	Mucus+ Bile+	33	13	0·002	Normal	67	51	Nil	Normal control
73	26	M	80	Mucus+ Bile+	33	17	Nil	Normal	46	33	Nil	Normal control

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CALCIUM AND PHOSPHORUS METABOLISM IN CHRONIC DIARRHOEA WITH TETANY [1]

BY G. C. LINDER AND CHARLES F. HARRIS
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DIARRHOEA has figured amongst the causes of tetany from the time when tetany was first defined. Trousseau (1), in a lecture in which he described the sign to which his name has been given, referred to tetany as a complication of diarrhoea, 'especially when abundant and chronic'. In this century many accounts of the association of tetany with diarrhoea have appeared, and it seems probable that in many cases the diarrhoea, especially 'when abundant and chronic', accompanied gross anomalies in the absorption of fat.

Of the common causes of defective fat absorption, pancreatic disease and obstructive jaundice do not appear in the reports of tetany; and it is probable that relief by operation or termination by death must prevent these grave conditions from persisting for a sufficiently prolonged time. It has not been reported in pancreatic infantilism.

The steatorrhoea which sometimes accompanies tuberculous peritonitis is caused by obstruction of the lacteals by caseous deposits in the mesenteric glands. Ryle (2) has described such cases, in one of which tetany was present. He suggests that a similar pathology of inflammatory lymphadenitis and lacteal obstruction may underlie the steatorrhoea of sprue and coeliac disease.

Tetany is a well-recognized if somewhat rare complication of tropical sprue. It appears to have been reported first in 1913 by Cantlie (3), who stated that he had seen it in six cases, and that such attacks did not foretell a fatal issue. It was rediscovered in 1919 by Bassett-Smith (4), who recorded one case of very severe tetany occurring in the days immediately preceding the patient's death. The first chemical study was made by Barach and Murray (5) in 1920 in a case which was complicated by vomiting, appendicitis, and fatal peritonitis. Since the vomited material was not acid, and since there was not an alkalosis, it appeared that the vomiting was not the cause of the tetany. The serum calcium was 8·0 mg. and later 6·5 mg. per cent.; the authors ascribed the tetany to this, and attributed this low state of the serum calcium to defective absorption from the fatty intestinal contents and to excessive elimination of calcium by the gut under the stimulus of the diarrhoea. Scott's (6) reports of the benefit derived from the treatment of sprue with calcium salts and parathyroid extract by mouth focused attention upon the metabolism of calcium in sprue; he observed

[1] Received October 7, 1929.

that the serum calcium was diminished in late or severe cases, and that tetany, particularly in its milder manifestations, was not uncommon. Ashford and Hermandez (7) agreed that calcium deficiency occurred in sprue, although in more than half of their severe and cachectic cases the serum calcium was normal; they found calcium deficiency of equal or greater degree in other diseases and in simple malnutrition in the tropics. Collip's parathormone they found of use in the treatment of tetany and cramps, but not otherwise of value. Bovaird (8) and Baumgartner (9) report further cases of tetany with low blood calcium in sprue.

Gee (10) described a peculiar weakness of the legs in the coeliac affection, but not the bone changes or tetany, which, however, are not uncommon. The bone changes comprise a general lack of calcification with poor development of compact bone and trabeculae; lack of growth prevents the occurrence of the epiphyseal changes characteristic of rickets, to which the bone condition is closely allied. Parsons (11) has studied the inorganic metabolism in coeliac disease, and found that the serum calcium was low, 6 to 9 mg. per cent., and that the serum inorganic phosphorus was reduced to 5 or 4 mg. per cent., and occasionally to a yet lower figure. Langmead (12), in 1911, recorded fourteen cases of tetany with dilatation of the colon, pultaceous, pale, offensive stools and stunted growth; these cases appear to have included samples of coeliac disease. Langmead attributed the tetany partly to toxic absorption from the putrefying contents of the colon, but also to some other factor, such as a defect in the protective mechanism. Lichtenstein (13) recorded tetany in four out of a series of nine cases.

Finally, less defined cases of fatty diarrhoea and tetany have been recorded in adults, accompanied by extreme malnutrition and wasting. They occur sporadically in temperate regions, and have been regarded by some as non-tropical sprue, although Monilia psilosis is not found in the stools, and by others as coeliac disease developing in or persisting into adult life. Gee (10) said of coeliac disease, which he did not clearly separate from tropical sprue, ' Seldom is it met with in adults who have never left our island'. Findlay and Sharpe (14) described in 1919 the case of a man who had coeliac disease in childhood and recurring diarrhoea and tetany in adult life; nutrition was seriously affected, and his greatest weight had been only 84 lb. Tileston and Underhill (15) reported a similar case. Blumgart (16) described three cases of fatty diarrhoea with anaemia, emaciation and tetany; the serum calcium in one of these was 5·3 mg. per cent. shortly before death, and at autopsy the intestinal mucous membrane showed numerous gray punctate elevations which were composed of phagocytes laden with fat. Snell and Habein (17) recorded another case in 1928, and gave a full review of the literature of this subject. Holmes and Starr (18), 1929, collected five cases with the further complication of severe anaemia.

Methods and Material.

The observations recorded in this paper were made upon two women with fatty diarrhoea of the endemic type and upon a third who was in a late stage of recovery from tropical sprue. Determinations were made of the calcium (19), inorganic phosphorus (20), and carbon dioxide (21) of the serum. The serum for the phosphorus was obtained by immediate spinning to avoid unnecessary contact with the clot and red cells. At first our resources permitted only of intermittent observations on the calcium balance, which did not prove satisfactory. In the later studies continuous analyses of stools and urine were made for calcium and phosphorus. The stools were collected over periods of four or more days, the periods being marked off with carmine. Being fluid they were readily mixed by stirring, and a small sample was taken for drying. The dried sample was ground in a mortar and ashed by the Stolte method (22). On dissolving the ash in hydrochloric acid the heating was prolonged in order to convert any metaphosphoric acid to orthophosphoric acid. The calcium was determined by the method of Tisdall and Kramer (23) and the phosphate by that of Fiske and Subbarow (20). The calcium in the urine was determined in a similar way, but the phosphate was estimated directly in 48-hour specimens of urine preserved in the cold with toluol. Constant weighed diets were given to the patients, the calcium and phosphorus contents of which were calculated from the tables of Sherman (24) ; the more important articles in the diet we analysed and found that agreement with Sherman's figures was close.

The results are recorded in Charts I to V and in the Table on page 212. The bulk of the metabolic data prevents its being given in full in table form, but the agreement of the individual periods can be seen from the charts. In reading the calcium and phosphorus balance on the charts it should be noted that the heavy horizontal line represents the intake measured from the base line ; the irregular line bordering the shading represents the total output, also charted from the base line ; and the shaded areas represent the balance—the lighter shading a positive balance, and the darker a negative.

Clinical Histories and Experimental Data.

Case I. Mrs. C., aged 33, was admitted to hospital on February 28, 1927. Her history was that in childhood her abdomen was enlarged, and that then and since her stools had been bulky, fluid, pale, and offensive. Five years before she had had pneumonia, which was followed by ill-health and amenorrhoea. Four years before she had begun to have cramp in the hands and feet, and later attacks of 'hoarseness and hard breathing' and spasm of the eye muscles. At the time of observation she was having three severe attacks of tetany, including laryngismus, in a week and frequent minor attacks. She was quite disabled. She complained of much pain in the legs and back with weakness and stiffness which was attributed to the tetany. She had been married for two years and had not been pregnant.

On examination she was a small person of poor physique and marked thinness ; her height was 4 ft. 9 in.—she had well-marked dorsal kyphosis—and her

weight 76 lb., the normal weight for her height and age being 115 lb. (Tables of
the Actuarial Society of America). The signs of tetany were obvious. The
abdomen was not enlarged and no viscera were palpable. The pelvic colon was
enlarged, as shown by barium enema. The stools were very large, liquid, and
extremely offensive; their fat content is shown in the Table on page 212. The
Wassermann was negative; the blood count: red cells 4,820,000, white cells
12,400, and haemoglobin 85 per cent. Cerebrospinal fluid normal. Standard
metabolism, −8 per cent.
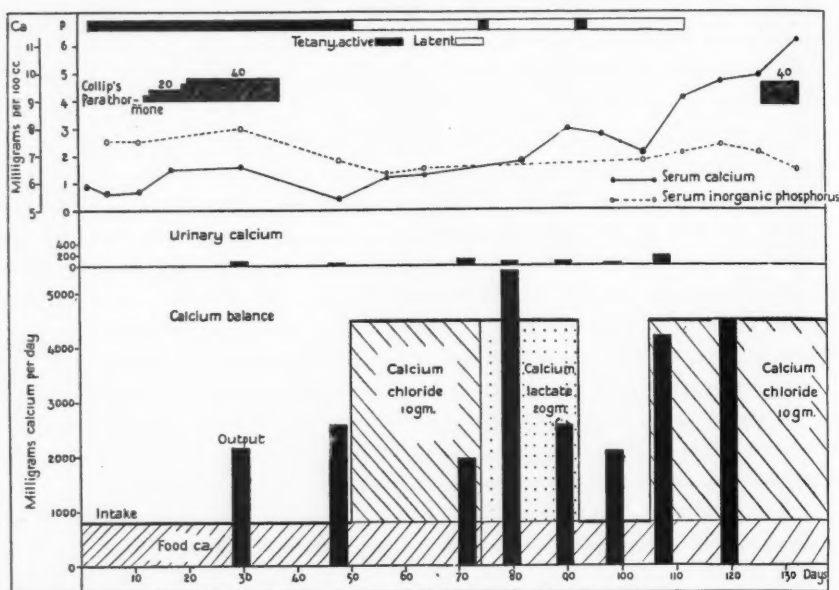
CHART I. Data obtained from Case I during first observation period. In order from
above downwards are shown the presence of tetany, the serum calcium, and inorganic phos-
phorus, and the calcium intake by the continuous horizontal line, and the output by the
separate rectangles.

Chart I is a record of observations made at this time. The serum calcium
was 5·7 mg. per cent. and the inorganic phosphorus 2·5 mg. per cent.; [1] the carbon
dioxide content 70 volumes per cent. After a short period of observation,
throughout which tetany was continually present, a trial of Collip's parathor-
mone was made; the dosage was started at 10 units hypodermically, increased
next day to 20 units, and after a week to 40 units a day, at which rate it was
continued for 17 days. This treatment had no effect at all on the tetany; the
serum calcium was raised to 6·7 mg.; and since it fell to 5·4 after the parathor-
mone was discontinued, it must be assumed that the parathormone was
responsible at least for this effect. Owing to difficulties in supply, it was not
possible to use larger doses. The calcium balance was negative during this
period.

After a period without treatment calcium chloride was given in doses of
10 grm. a day by mouth. The effect on the tetany was remarkable, for in the
course of a day the tetany disappeared, although Chovstek's sign could still be
elicited, and the electrical reactions remained characteristic of tetany. This

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[1] The normal serum calcium is from 9·5 to 10·5 mg. and the normal inorganic phosphorus
in adults from 3·5 to 4·5 mg. per cent. (25).

effect may be obtained regularly in infantile tetany by giving acid-forming salts, such as ammonium chloride, and is probably due to the effect of the changes in acid-base balance on calcium ionization (26).   That this was the case here was shown by the lack of marked effect on the total serum calcium, which after 13 days' treatment had risen to only 6·3 mg., whereas the acidosis was confirmed by observations of the acid-base conditions in the arterial blood, as described by Fraser, Hilton, Harris, and Linder (27), and recorded in Chart II.
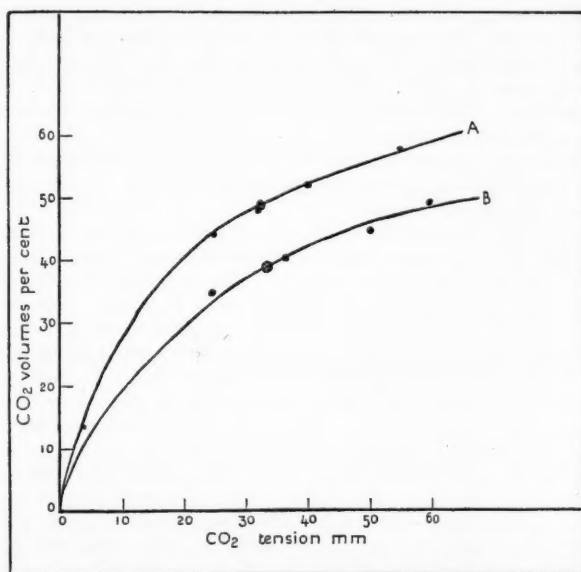
CHART II.   Acid-base conditions in the arterial blood of Case I before (A), and after 18 days' treatment with calcium chloride, (B), showing the production of acidosis.   The level of the CO_2 tension—CO_2 volume curve is lowered, the arterial pH changes from 7·43 to 7·35, and the arterial CO_2 content from 48·5 to 39 volumes per cent.

After three weeks the calcium chloride was changed for calcium lactate in a dose, 20 grm. a day, containing an equivalent amount of calcium.   Tetany at once recurred, the cause probably being the readjustment of acid-base balance. It disappeared again in a few days, when the serum calcium had risen to 6·8 mg. ; 10 days later it had reached 8·0 mg.

On stopping the lactate tetany again appeared for a short period and the serum calcium began to fall.   The body was losing calcium.   Calcium chloride was given again, and the serum calcium increased again, reaching 9·1 mg.   After this considerable period (63 days) of heavy calcium treatment, during which our figures indicated the probability of considerable calcium retention, it was decided to try the effect of parathormone : the result was a brisk response with a rise from 9·6 to 11·2 mg. after 4 days on 40 units a day.

The serum phosphorus, after rising to 3 mg., when the parathormone was first given, fell to 1·4 mg. just after the calcium chloride was started ; after this it showed a tendency to increase, but the highest figure reached was 2·3 mg. during the second period of calcium chloride treatment.   Since phosphate has an inhibitory effect on calcium ionization (28), and is therefore a factor increasing the liability to tetany, this low phosphorus concentration was viewed with complacency.

The patient greatly improved during this period. Her weight increased to 82 lb. The tetany had gone, and she was able to read and sew. She complained more and more that walking and sitting were difficult and painful; the hips and knees were freely movable, there were no changes in the reflexes, and no local wasting of muscles. The condition was thought to be a residue from the tetany, and was tested with massage and exercises.

She went home in July, 1927, and was to take 3 grm. of calcium chloride a day. Minor tetanic phenomena appeared, and the calcium salt was increased to 6 grm. The serum calcium remained in the region of 9 mg. and the inorganic phosphorus at 2 mg. Her complaint of pains in the legs and back became more insistent, the massage had to be stopped, and it was obvious that she was becoming more and more crippled. Her general health deteriorated, and she lost a stone in weight. Examination showed that the lumbar spine had become straight and rigid, and that there was no rotation of the vertebrae; there was great tenderness over the spine, not localized to any particular vertebra, and also over the lower ribs and the crests of the iliac bones. An X-ray of the spine showed no arthritis or tuberculosis.

The patient was readmitted in March, 1928. A series of skiagrams were taken which showed very poor shadows of the bones generally, but particularly of the pelvis, vertebrae, and ribs; many of the last were fractured. Two explanations of this state presented themselves. Was this the result of the persistent treatment with calcium chloride, an acid-forming salt? And had calcium actually been abstracted from the bones to enable this acid to be excreted? It will be seen from Chart I that the urine calcium was highest when the calcium chloride was being taken, but on the other hand the total calcium balance was positive. The second possibility was that this decalcification was part of the original disease, possibly a coeliac rickets, or osteomalacia. The low level of the serum phosphorus when this patient was first observed, and the fact which was now elicited that stiffness and pain on movement in the shoulders, backs, and legs had come on with the tetany and had progressed steadily since, may be urged in support of this view. In any case it seems most probable that the calcium chloride still further prejudiced the retention of phosphorus both by interfering with its absorption and by creating a demand for the excretion of acid phosphate to maintain normal acid-base balance.

At the time of re-admission the balance of calcium and phosphorus was positive, as shown in Chart III. After eight days, to observe this fact, calcium lactate was given instead of the chloride, and to the diet was added casec (a powder containing 88 % protein, prepared by Mead, Johnson, & Co.), to increase the phosphorus intake without increasing the fat; phospho-protein appeared more suitable than inorganic phosphate for this purpose, since the latter with the calcium might have formed insoluble calcium phosphates in the intestine. Ultra-violet light therapy was also commenced. Under this treatment the serum calcium was maintained, while there was a slow but quite definite rise in the serum phosphorus; the balance of phosphorus showed an increasing bias to retention, although periods of loss did occur, and the balance of calcium showed a large and increasing retention.

In spite of this degree of chemical improvement the clinical state of the patient changed very little. From the 52nd day 18,000 units (29) of irradiated ergosterol were given daily. The rise in serum phosphorus continued, but its rate of increase did not change; a figure of 5·6 mg. was obtained on the 72nd day. The positive balance of calcium and phosphorus was now confirmed. As there was still little improvement in the patient and no appreciable change in the radiograms of the bones the dose of ergosterol was doubled. Improvement in the patient very slowly became apparent; the great tenderness disappeared and walking ceased to be a torture. At the time of discharge in July, 1928, she was very definitely improved, and some increase in density of

the bones was apparent. The tetany remained absent but Chovstek's sign was occasionally positive. Her weight was 72 lb.

During this second period of observation the urine phosphorus, though low to begin with, 80 mg. a day, fell yet lower, and from the 16th to the 32nd days varied from 15 to 30 mg. a day: the total output was 700 mg. a day, and in normal persons half of this would have been excreted in the urine. This low urinary excretion we attributed to the serum inorganic phosphorus being under
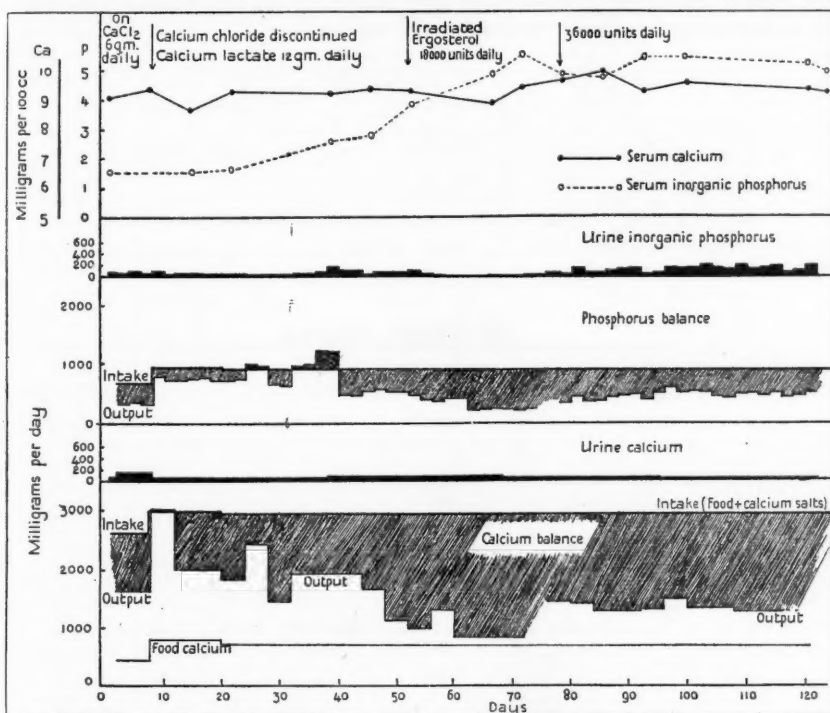
CHART III. Data from Case I during second observation period. The heavy horizontal lines represent the calcium and phosphorus intakes, the irregular line bordering the shading represents the total output, and the shaded areas represent the balance, the lighter shading a positive balance, and the darker a negative.

2·0 mg., which is less than the threshold (30). With the commencing rise of the serum phosphorus the urinary phosphorus increased, but fell again to less than 20 mg. from the 55th to 70th days. At this time the serum phosphorus was much higher and definitely above the threshold, which is at a level of about 2·8 mg. per cent. The ergosterol was begun on the 52nd day, and may have been the factor concerned in this second fall. After this the urine phosphorus increased to approximately normal amount.

Case II. Mrs. E., aged 28, was admitted to hospital on August 14, 1928, with a complaint of abdominal pain, chronic diarrhoea, and extreme wasting. She dated her troubles from the time of her marriage two years before, since when she had never been well, had had frequent attacks of diarrhoea, and recently had become emaciated and very feeble. Her menses had been regular till they ceased about four months after her marriage, but she had not been pregnant.

On admission she weighed 67 lb. She had been a buxom woman, 5 foot tall, and weighing 140 lb., so the emaciation was extreme. The heart and lungs were healthy. The abdomen was distended, but no viscera could be felt. Clubbing of the fingers was well marked. The legs were wasted but without oedema. Blood count: red cells 3,680,000, white cells 3,600, and haemoglobin 81·3 per cent. Test meal showed normal acidity. Wassermann, negative. The stools were bulky. When a few days later she had an attack of tetany, and the analysis of the stools showed their fatty nature, it was realized that this must be a condition very similar to that studied in Case I.
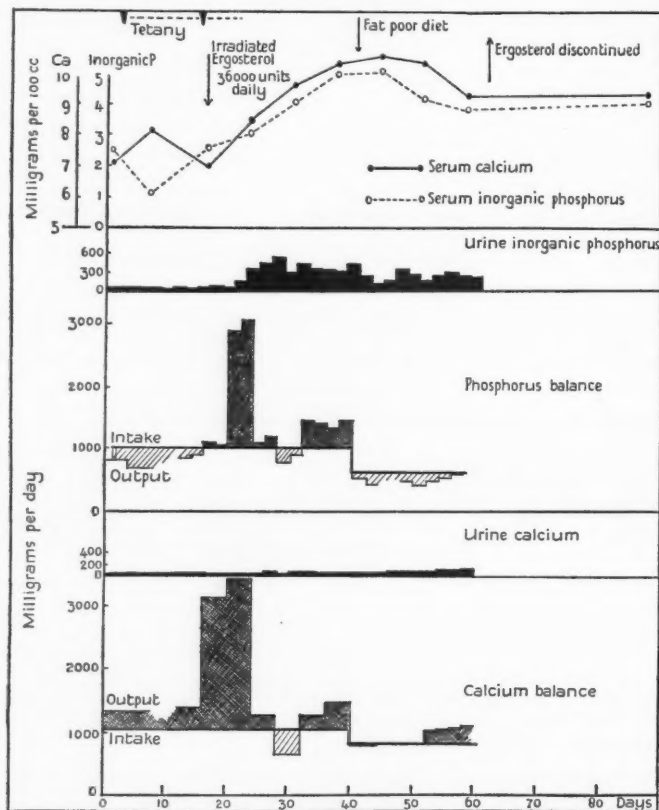
CHART IV.   Data from Case II.

Chemical examination of the serum confirmed this resemblance. The serum calcium was 7·1 mg. per cent., the inorganic phosphorus 2·5, and the carbon dioxide 73 vols. per cent. The urine phosphorus was 20 to 30 mg. a day, the total excretion being 700 to 800. On a diet containing a liberal supply of calcium and phosphorus there was a small negative balance of calcium and a small positive balance of phosphorus.

She recovered from her attack of tetany, but Chovstek's sign remained active. Fourteen days later there was another attack of tetany, and from the following day 36,000 units of irradiated ergosterol were given daily. Chart IV shows the immediate and striking response. Five days later Chovstek's sign had disappeared. In seven days the serum calcium had risen to 8·5 mg. and

the phosphorus to 3·1 mg.; in fourteen days to 9·8 and 4·1, and in a month to maxima of 10·6 and 5·1.

The changes in calcium and phosphorus balance were striking and unexpected. Over the eight days following the first day of giving ergosterol there was a negative balance of calcium averaging 2,050 mg. a day, the negative balance in the preceding periods having been 300 mg. a day. A similar excretion of phosphorus occurred in the period from the fifth to eighth days following the ergosterol, when a positive balance of 180 mg. a day was changed to a negative balance of 1,960 mg. a day. In both cases the major part of the excess excretion was by the gut. This excessive excretion was a temporary phase, and disappeared as rapidly as it had appeared.

The urinary phosphorus rapidly increased a week after the ergosterol to a normal level. The urine calcium increased from 20 to 100 mg. a day.

The patient was much more comfortable during this period and gained 10 lb. in weight, but she continued to pass enormous fatty stools. On the 41st day the fat in the diet was reduced from 100 grm. to 30 grm. a day. Table I shows that the fat lost in the stools fell from 30 grm. to 10 grm. a day. The stools became much less bulky, although still offensive and unformed. From this time onwards the patient's weight and general condition improved in a most dramatic way: her weight increased to 84 lb. before she left hospital, and four months later, by continuing the same diet at home, she attained a weight of 118 lb.

Three months after leaving hospital the patient started to menstruate normally: by that time she had had amenorrhoea for nearly three years. Two months later again, after her second period, she became pregnant.

On leaving the hospital the ergosterol which she had taken for forty-five days was stopped. There was no return of tetany throughout the winter and the calcium and phosphorus in the serum remained high. There was no evidence of decalcification in this case.

Case III. Miss N., aged 38, contracted sprue in India in 1926 and was invalided home the following year. She recovered her general health but continued to have mild diarrhoea with occasional exacerbations. At intervals during 1927 and 1928 she noticed tingling of the hands and feet, which sometimes became stiff. On November 26, 1928, she came to hospital with an attack of tetany, which lasted for an hour; the diarrhoea had not been worse than usual.

On examination she was a small person, thin but not emaciated, weight 76 lb., and rather pale complexioned. When the attack of tetany had passed Chovstek and Trousseau's signs were negative. The tongue was clean, dry, and the papillae were atrophied; earlier in her illness the tongue had been sore. The heart and lungs were healthy. The abdomen was slightly distended, but no viscera except the right kidney were palpable. There was slight inactive clubbing of the fingers. The stools numbered two to four a day; they were light coloured, bulky, fluid, but not frothy and offensive. For the fat content, see Table I. She had had amenorrhoea since 1927. The Wassermann was negative.

The serum calcium was moderately low, 7·7 mg. per cent., and the serum inorganic phosphorus was on three occasions less than 2·0 mg. per cent. On a diet low in calcium and phosphorus the balance of phosphorus was positive and that of calcium negative. The urinary phosphorus excretion was 100 to 150 mg. a day out of a total excretion of 400 to 500 mg. The carbon dioxide content of the venous serum was 68 volumes per cent.

The attacks of tetany continued and were provoked by psychical stimuli, such as the sight of a muscle-testing apparatus. Chovstek's sign was occasionally positive but often negative, and the electrical reactions taken during a severe attack of tetany failed to show polar reversal.

Irradiated ergosterol was given in the expectation that results similar to those obtained in Case II would be repeated. The serum calcium rose to 8·8 mg. in seventeen days but subsequently showed a definite tendency to fall. The phosphorus increased slowly to 3·0 mg. There was no large output of calcium or phosphorus as in Case II ; in fact there was no change in the balance. On the 53rd day, after 35 days on ergosterol, a diet higher in calcium and phosphorus was given, with the result that a positive daily balance of about 600 mg. each of calcium and phosphorus was established. In spite of this the tetany became more frequent and severe, and the serum calcium and phosphorus fell again to 7·3 and 2·0 mg. respectively.
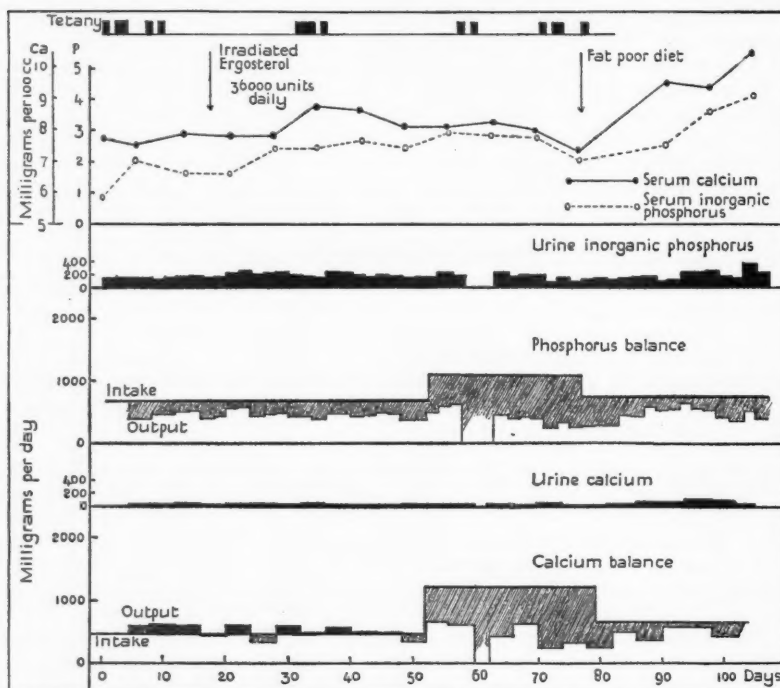
CHART V. Data from Case III.

On the 78th day a change was made to a diet containing only 15 grm. of fat. The tetany disappeared two days later, and soon after the serum calcium and phosphorus rose to normal figures ; the patient's condition apart from the tetany improved strikingly, the intestinal condition improving. and her will to attempt to do things returning, she gained a little weight. The fat-free diet contained less calcium and phosphorus, but the total excretion remained the same, so that the balance, although still positive, was smaller than in the preceding period.

The Steatorrhoea.

Table I gives the results of the fat analysis of the faeces in the three cases. The fat utilization was exceedingly low in Case I during her first admission, much less than in the other cases. This was associated with the extreme size of

the fluid stools, in which a litre of water alone was lost a day; Garrod (31) has described these stools as elephantine. This exaggerated condition may perhaps be associated with the greater length of the patient's illness and its greater severity. The remaining analyses showed severe but more usual defects in fat utilization.

There was no evidence of defect in fat splitting. When the fat wastage was lowest the proportion of neutral fat lost was increased. The soap content in many of the analyses was very small; the amount of calcium which could have been lost if all this soap was calcium soap is given, and shows that in Case I it could never have been more than a quarter of the calcium of the stool; in Case II it formed an insignificant part, while in Case III it was considerably higher until the fat intake was reduced. The calcium utilization has a rough relationship to the total fat output, being high only when the fat excretion was low. A low fat intake appeared to be an important factor contributing to the prevention of excess fat excretion but not essential to good calcium absorption, provided that the larger amount of fat was itself coped with efficiently.

Amenorrhoea.

It will be observed that each of these patients suffered from amenorrhoea, of five years' duration in one instance, eighteen months' in another, and two years' in the third. Neither of the two married patients had become pregnant while this symptom was present. In Case II, four months after the return of the blood calcium and phosphorus to their normal levels, the menses recommenced, and within a short time the patient became pregnant.

It does not appear likely that a disturbance of ovarian function was the primary defect in these women and that the disturbance of calcium metabolism and tetany followed on this; for in every case the amenorrhoea appeared as a symptom after the steatorrhoea had become established, and in Case II menstruation recommenced some months after other abnormalities had disappeared. There are two other possible explanations. Either the amenorrhoea occurred solely as a result of the general ill-health of the patients, or it was due much more directly to the altered calcium metabolism and the decrease of calcium in the blood. We do not think that any final conclusion can be reached from the observations on these three patients; but in view of the well-recognized inter-relationship between calcium and ovarian activity it seems probable to us that the latter hypothesis will provide an explanation of the amenorrhoea in such cases.

Discussion.

The conclusions of other workers as to the nature of the tetany appearing in the fatty diarrhoeas may be briefly recapitulated. Langmead (12) ascribed it to a toxaemia from the stagnant putrefying bowel contents acting in

conjunction with a defect in the protective mechanism or a special infection. Barach and Murray (5) attributed it to calcium deficiency from interference with calcium absorption by the excess of lipids in the stools and from excessive elimination of calcium due to irritation of the gut by the diarrhoea. Underhill, Tileston and Bogert (32) demonstrated a greater need of calcium and unstable calcium equilibrium in their case. Findlay and Sharpe (14), in a case of adult tetany, found a subnormal retention of calcium associated with a diminished absorption of fat. The excretion of guanidin bodies in the urine was increased. Telfer (33) found grossly defective absorption of mineral elements and fats in a case of coeliac disease. Critchley (34) believed that a disturbance of nitrogen metabolism is the basis of all forms of tetany, but added: 'It is conceivable that tetany when arising in conditions of chronic diarrhoea is due primarily to non-assimilation of vitamins.' Parsons (11) says of coeliac rickets: 'The cause is to be found in defective fat absorption with resultant defective absorption of vitamin D, calcium, and phosphate.'

From the data recorded here, and by other workers, it appears certain that the tetany has its basis in a deficiency of calcium in the serum; in this it resembles the tetany of parathyroid deficiency and osteomalacia and infantile tetany. It further resembles the last two of these in being accompanied by a decrease in serum inorganic phosphorus and by a tendency to impaired calcification of bone. In these points it is in contrast with parathyroid tetany in which the phosphorus in the serum is high (35) and decalcification absent; on the contrary the serum phosphorus is reduced by a sufficient dose of parathyroid extract (36), and calcium excretion is increased (37), while excessive doses will cause decalcification (38, 39, 40). It is unlikely, therefore, that a simple functional insufficiency of the parathyroids due to toxaemia could furnish a full explanation of the facts.

Perhaps the most obvious way of accounting for the want of calcium and phosphorus is to assume that their absorption is interfered with by the diarrhoea and excess of lipids in the stools. Acute diarrhoea undoubtedly prejudices absorption. Diarrhoea may also lead to excessive excretion of calcium by irritation of the gut (5); Luckhardt and Compere (41) showed that parathyroid-ectomized dogs kept out of tetany by calcium salts could be thrown into tetany by drastic purges. The diarrhoea in our cases was by no means drastic, for although the motions were large and liquid the movements of the bowels occurred only once to thrice a day; it appeared that at the time the malabsorption was the primary event and the looseness of the bowels the secondary.

There is more evidence that the defective absorption of lipoids is an important factor, as suggested by Barach and Murray (5) and by Ryle (2). Telfer (42) correlated the absorption of calcium and phosphorus with that of fat in children. He inferred that when the stools contained excess of fat, calcium was bound as insoluble calcium soap and escaped absorption; normally the excess of calcium combined with phosphate, and therefore in the fatty diarrhoeas,

a surplus of phosphate remained and was absorbed; but since phosphate could not be retained without calcium it was re-excreted into the urine. In accord with this he found in such cases the ratio of urinary to faecal phosphorus to be greater than normal. Telfer concluded that the absorption of phosphorus was always adequate but that its fixation in bone depended on a sufficient absorption of calcium. The facts in our cases do not agree with this hypothesis, for the serum phosphorus was more deficient than the calcium and the urine phosphorus was remarkably low. Telfer's own observation in a case of coeliac disease (33) confirms the latter finding, for although half the lime of the faeces existed as calcium soaps the ratio of urine to faecal phosphorus was only 1 to 2·7 ; he was therefore forced to postulate a further defect in mineral metabolism affecting the absorption of phosphorus.

Telfer assumed that no important part of the calcium intake was absorbed and re-excreted into the gut, and his interpretation of his results is contingent upon the truth of this assumption. Salvesen (35) showed that after intravenous injection of calcium salts into parathyroid-ectomized dogs, 80 per cent. of the injected calcium was excreted into the gut in twenty-four hours. Stewart and Percival (43) established that in cats the main excretory route is by way of the large intestine. Bergheim (44) showed that in rats there was a considerable secretion of phosphate into the upper intestine which apparently promoted the absorption of calcium; this agrees with the views of Van Noorden (45) on the mechanism of calcium absorption. Bergheim found that rats with healing rickets absorbed calcium throughout the intestine and reabsorbed the secreted phosphorus from the large intestine, but that if the rickets were active, calcium was excreted into the large intestine and the phosphorus was not reabsorbed. He concluded that the essential fault in rickets lay with the low level of serum phosphorus which prevented the deposition of the absorbed calcium as bone, and that antirachitic substances acted by promoting the breakdown of organic tissue phosphorus and raising the blood phosphorus. The extent of the normal re-excretion of calcium into the gut in man awaits direct proof, but our opinion is that Stewart and Percival's observations are of great significance, and that the re-excretion is considerable.

Holt, Courtney, and Fales (46) found no relation between soap and calcium excretion in infants, but in children there was some relation between them although the calcium excreted as soap was an insignificant part of the intake. In chronic intestinal indigestion the absorption of calcium was very low, and the excretion of fat and soap was high but not parallel with the calcium excretion. In a few of these cases, in which the fat and calcium was high, calcium excretion was normal.

The small amount of soap in many of our faecal analyses shows that, except in Case III, calcium soaps could not have been an important factor in preventing calcium absorption. The weight of evidence is therefore against the formation of calcium soaps being the cause of the calcium deficiency, but the association of better calcium utilization with decreased fat excretion suggests

that the fat may physically interfere with calcium absorption or that changes in intestinal absorptive power affect both substances independently.

The possibility of a vitamin deficiency remains for consideration. The data in our opinion afford a reasonable basis for the supposition that failure to absorb vitamin D is the chief factor concerned. This deficiency may be remedied by giving very large amounts of the vitamin, but, in addition to this, it may be necessary to facilitate absorption by drastic fat restriction.

The points we would recall in this connexion are: (1) The remarkable effect of irradiated ergosterol on the tetany and serum chemistry in Case II and the immediate change in the calcium and phosphorus balance. (2) That in Case III the ergosterol was practically without effect until the fat-poor diet was instituted, and that then the tetany disappeared and the serum chemistry became normal; these facts cannot be explained on the supposition that fat restriction had promoted calcium and phosphorus retention since the established positive balances were considerably diminished. (3) Except for the immediate and passing effect in Case II the effect on the calcium and phosphorus balance of giving ergosterol, if necessary coupled with fat restriction, was remarkably small, whereas the changes in the patients and their sera were swift and striking; the decisive action was therefore to enable the serum to hold a larger amount of calcium and inorganic phosphorus, which is exactly the effect of vitamin D (44).

It may be urged against this conclusion that in two of the three cases 60 to 90 per cent. of the fat was absorbed, but it is still possible that the deficient moiety may have contained the sterols. This aspect of the subject might repay investigation. Holmes and Starr (18) have reported five cases differing from ours in having severe anaemia of pernicious type; the tetany was relieved by parathormone but not by cod-liver oil; ergosterol was not tried. The failure with cod-liver oil may have been due to the same factor as operated in our Case III, namely, non-assimilation of the vitamin from the excess of intestinal lipoids. These authors attached but secondary importance to fat restriction in the diet, whereas we would put it in the first place.

The immediate effect of irradiated ergosterol in Case II in causing a great excretion of calcium and phosphorus has a bearing on the mechanism of action of this vitamin. The ratio of calcium lost, less 10 per cent. for carbonate calcium, to phosphorus lost over this period of eight days was 1·97; the value of this ratio for the inorganic components of bone was found by Shear and Kramer to be $2·00 \pm 0·06$ (47). Probably bone supplied the calcium and phosphorus in our case. Except for its fleeting nature this action was identical with that of para-thyroid hormone (38, 39, 40), and supports the conception that the vitamin may be necessary to the proper action of the parathyroid glands. Evidence pointing in the same direction has been presented by Jones (48) and Brougher (49), who showed that cod-liver oil could to a large extent prevent the onset of experimental parathyroid tetany.

The lack of inorganic phosphorus in the serum appears to be as character-

istic of the condition as the lack of calcium. Blumgart (16) recorded low serum inorganic phosphorus in his cases, but others have paid little attention to it. The deficiency of phosphorus was probably the more important factor in the decalcification in Case I. The scanty excretion of phosphorus in the urine in Cases I and II is accounted for by the fact that the serum inorganic phosphorus was below the threshold of 2·8 mg. per cent. ; that this threshold is not a strict one was shown by the continued excretion of phosphorus (10 to 25 mg. a day) at a level of 1 mg. per cent. in the serum and by the comparatively large amount excreted in Case III at a level below 2 mg. per cent. That vitamin D or the rising calcium or phosphorus in the serum may have had some influence on the threshold is suggested by the renewed fall in urine phosphate in Case I when ergosterol was given on a rising tide of serum phosphorus.

Treatment.

The importance of fat restriction in the diet of patients with excess of fat in the stools has been urged by Ryle (2) and many others. This important step in treatment is apparently often omitted. Our experience has shown that it may be an essential step in the treatment of their tetany and that it is of the greatest consequence in the restoration of a normal state of nutrition.

The opportunity has not presented itself to test the idea that fat restriction alone would permit recovery from the tetany to occur, and this may not be the case since the general restriction of fats would restrict the natural sources of vitamin D. Probably it is necessary to give this vitamin at the beginning of treatment unless recovery is to be unduly delayed, but as shown in Case II, when recovery has occurred, fat restriction alone may suffice to maintain a normal vitamin balance. Irradiated ergosterol is probably superior to cod-liver oil in these cases.

'Acid-forming' salts such as calcium and ammonium chlorides, although very efficacious in relieving tetany, are undesirable for prolonged use in chronic cases in which the serum inorganic phosphorus is at a low ebb. If they are used, skiagrams should be taken at intervals to guard against decalcification. Calcium lactate may be of benefit in cases in which a positive calcium balance is desired with the object of promoting calcification, but its use is not necessary in other cases if adequate diet and vitamin supply be established.

Summary and Conclusions.

1. Clinical and biochemical studies are reported of three cases of tetany occurring in adults with fatty diarrhoea.

2. The immediate cause of the tetany was calcium deficiency.

3. The serum inorganic phosphorus was reduced to a very low level, and in two of the patients phosphorus was almost absent from the urine.

4. In one case decalcification of bone and spontaneous fractures occurred.

5. From consideration of the calcium and phosphorus balance, the soap and total fat excretion, and the response to treatment, it seemed that the cause of the condition was deficiency of vitamin D. The physical effect of the fats in impeding calcium absorption may have played a minor part.

6. The action of irradiated ergosterol in one case resembled that of parathyroid extract in causing a mobilization of calcium and phosphorus from the bones and in increasing their excretion.

7. Treatment by fat restriction and large doses of irradiated ergosterol was effective. Fat restriction may be essential to adequate absorption of the ergosterol, besides being desirable from the standpoint of the general nutrition of these patients.

8. The possibility of causing decalcification by the prolonged administration of calcium chloride or other acid-forming salt is suggested.

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TABLE

Date	Day of Observation	Fat Intake grm./day	Fat Output grm./day	Fat Utilization %	Calcium Intake grm./day	Calcium Absorbed grm./day	Calcium Utilization %	Fat % of Dry Weight	Water Content of Faeces grm./day	Neutral Fat grm./day	Fatty Acid grm./day	Soap grm./day	Maximum Calcium Excretion as Soaps grm./day	Calcium in Faeces grm./day	Soap Calcium as % of Total Calcium
Case I															
27.4.27	—	84	73	13	4·440	—	—	68	950	25	34	14	1·000	—	—
12.5.27	—	84	24	71	4·440	2·540	57	74	—	17·5	—	6·5	0·460	1·900	24
9.6.27	—	54	36	33	0·800	0	0	55	—	25	—	11·0	0·790	2·050	38·5
19.6.27	—	54	41·5	23	4·440	0·040	1	51	—	19·5	15·5	6·5	0·460	4·000	11·5
21.6.28	100	60	20·5	66	2·920	1·570	54	52	350	12	3·5	5·0	0·340	1·350	25
Case II															
28.8.28	1	100	16·7	83	1·050	0	0	51	140	9·7	6·2	0·8	0·060	1·280	5
1.9.28	5	100	31	69	1·050	0	0	60	260	18·5	12	0·5	0·040	1·280	3
21.9.28	25	100	28·5	71	1·050	0	0	48	460	14·1	10·5	2·9	0·211	1·200	17·5
15.10.28	49	30	10·5	66	0·820	0·140	17	31	200	7·3	2·1	0·6	0·040	0·680	6
Case III															
31.10.28	5	80	22	73	0·460	0	0	61·5	440	7·0	9·5	5·6	0·400	0·570	70
5.1.29	71	96	11·5	89	1·220	1·030	84	54	390	5·5	4·7	1·3	0·090	0·190	47
21.1.29	87	15	3·3	78	0·674	0·344	51	23·5	90	2·3	0·7	0·3	0·020	0·330	6

CRITICAL REVIEW :

THE LIVER TREATMENT OF ANAEMIAS [1]

By JANET M. VAUGHAN

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THE discovery, in 1926, that liver was an effective remedy in cases of pernicious anaemia was a powerful stimulus to those concerned either clinically or experimentally with the problems of blood destruction and production. As the result of much new work in this field our views as to the underlying patho- logy of anaemias have undergone considerable change. The present review is an attempt, in the first place, to assess the therapeutic value of liver in all forms of anaemia, and, secondly, to determine what light recent work has thrown on the pathology of such conditions.

For purposes of this discussion anaemias may be conveniently divided into the following groups :

1. Pernicious anaemia.

2. Anaemia associated with pregnancy or sprue and closely simulating pernicious anaemia.

3. Anaemia secondary to haemorrhage.

4. All ill-defined group of anaemias secondary to other conditions such as leukaemia or cancer or of unknown origin.

Group I. ⸱ Pernicious anaemia.

In the accompanying Tables I and II are collected the cases of pernicious anaemia that have been treated with liver, kidney, or extract—630 cases in all. Unfortunately of 255 of these full details are not available. The latter have been grouped together in Table I ; it will there be seen that only one case failed to respond, and he was moribund on admission. In the larger group, Table II, 16 cases only in a total of 345 failed to reach a red cell count of 3,000,000, 9 of these had only received treatment for a short period, and had all shown a definite improvement. One of the cases reported by Brewer, Wells, and Fraser had a negative Price Jones curve and so was probably a mistaken diagnosis ; one of the cases reported by Minot, one by Ordway and Gorham, and one by Vaughan had severe sepsis, leaving three patients only that showed an unex- plained failure to respond to liver after a long period of treatment, i. e. less than

1 per cent. of the total cases. Of fifty-four cases, 13·6 per cent failed to reach a red cell count of over 4,000,000. In many, this was due to unwillingness to take a sufficient quantity of liver, or to associated sepsis : 325, or 82·2 per cent., reached a red cell count of over 4,000,000, with an average haemoglobin percentage of 89, which satisfactory figure was maintained without relapse as long as liver was taken. When it is remembered that in 1925 pernicious anaemia was considered an incurable disease these figures are striking.

TABLE I. *Cases of Pernicious Anaemia treated with Liver in which Details of Improvement in the Blood Picture were not available.*

Reported by.	No. of Cases.	Successful Result.	Failure.
Abrahamson	4	3	1
Dyke	6	6	—
Fetter	34	34	—
Jenson	1	1	—
Jungmann	15	15	—
Langmead and Wilson	6	6	—
Maclean	4	4	—
Minot, Cohn, Murphy, and Lawson	160	160	—
Pal	1	1	—
Spence	22	22	—
Vemming	2	2	—
	255	254	1

Typical response. The nature of the response to liver feeding is so constant and has been so often described in the last four years that it need only be briefly discussed. Minot, as a result of a careful analysis of 150 cases, considers that within three to eight days of the administration of adequate amounts of liver or kidney in the form of fresh meat or extract there is an increase in the reticulocytes in the circulating blood reaching a maximum in the subsequent three to six days and then falling to normal levels. This is followed by a rise in the haemoglobin and total red cell count, reaching normal levels in about two months. 'Both the percentage and absolute number of reticulocytes in the peripheral blood at the peak of their rise are related to the level of the red blood corpuscles at the time treatment is begun ... up to the peak of the reticulocyte rise the increase in the concentration of total red corpuscles may be ascribed almost entirely to the production of reticulocytes when the red blood cells are less than 2,800,000. In cases which have received daily maximal amounts of potent extract for over twelve days the increase in the total concentration of red blood cells is dependent chiefly on the liberation from the bone marrow of mature corpuscles.'

Total white count. It is frequently claimed that the characteristic leucopenia is lost as a result of treatment. Unfortunately there are few actual figures given on this point. In a series of eighteen cases analysed by the writer, in eleven the count was approximately unaltered, being in eight cases below 5,000. In the remaining seven there was a definite increase in the total white cell count. Fleming has recently shown in watching a single case that

the Arneth polymorphonuclear count, which, in untreated cases, is shifted to the right, returns to the normal position after treatment. Too many conclusions must not be drawn from a single case, and the fact that the leucopenia is persistent in some suggests that the active liver fraction is unable to remedy completely the apparent defect in the production of leucocytes which is perhaps present in pernicious anaemia.

Eosinophils. It has been claimed by Whitby and Seyfarth that an eosinophilia is characteristic of the blood picture of patients receiving liver treatment. Whitby's figures are, however, not convincing. In only one did the eosinophil count rise above the highest limits of normal 400 per cm. In the other two though the percentage figure was raised the absolute figures were well within normal limits.

Weil, Pollet, Levy, and Flandrin do not draw any attention to the point, but two of their cases during treatment showed high eosinophil counts at intervals, in one case as high as 1,180, in the other 1,453. One of these cases showed figures on the upper limits of normal before liver was given. Ordway and Gorham state that eosinophils appear in greater numbers, but again give no details.

The writer in analysing the almost daily differential count of sixteen cases found no evidence for regarding eosinophilia as characteristic of the response.

Price Jones Curve. Since it is universally admitted that a shift of the Price Jones curve to the right is the surest diagnostic sign in pernicious anaemia it is important to know what effect liver treatment has on the curve. Medearis and Minot in eleven cases found that the mean diameter returned to normal, and in three cases less than normal. Davidson and McCrie on measuring five cases with blood-cell counts of over 5,000,000 found that excessive anisocytosis and megalocytosis were still present.

Price Jones in a series of twelve cases, in all of which the anaemia was cured, found that the red cell diameters and variabilities were brought towards or within the healthy range, but a completely normal position was only reached in six cases, irrespective of the length of treatment or severity of the condition. It is clear, therefore, that a return to a completely normal blood picture is not the uniform result of liver therapy. As Price Jones says, 'Considering that liver provides something which the body lacks and does not remove the cause of the disease, this is perhaps what we should expect'.

A sudden improvement in mental outlook and a rapid gain in weight are characteristic of satisfactory response to treatment. The mental improvement precedes the rise in the reticulocyte count. The gain in weight is most marked during the first month of treatment—it has been noticed by Wiel, Pollet, Levy and Flandrin, Ordway and Gorham, and Heath. The following table, from the writer's own series, illustrates this point.

It is unjustifiable to consider the anaemia apart from the other manifestations of the disease in endeavouring to determine the part played by liver as a therapeutic agent.

TABLE II. *Cases of Pernicious Anaemia treated with Liver, showing Details of Improvement in the Blood Picture.*

Reported by.	Before Treatment			R.B.C. under 3,000,000 after Treatment.			R.B.C. over 3,000,000 after Treatment.			R.B.C. over 4,000,000 after Treatment.		
	No. of Cases.	Red Cell Count.	Hb. %	No. of Cases.	Length of Treatment.	Hb. %	No. of Cases.	Length of Treatment.	Hb. %	No. of Cases.	Length of Treatment.	Hb. %
Aitoff and Leowy	1	1,560,000	27							1	2½ months	66
Anderson and Spriggs	2	1,050,000	29							2	1¼–2¼ months	94
Bubert	1	1,900,000	44							1	12 months	89
Brill	10	1,910,000	39				2	13 days	72	8	1¾–3½ months	87
Brewer, Wells, and Fraser	7	1,810,000	46	1	12 weeks. No improvement Price Jones curve +					7	3–8 months	95
	9	980,000		1	8 weeks. No improvement Price Jones curve +					9	3–8 months	
Crouzon, Mathieu, Gilbert-Dreyfus	1	1,740,000								1		
Davidson, McCrie, and Gulland	28	1,800,000	44	1	¾ month	70	6	½–1½ months	67	21	1–12 months	82
East	3						3	1½–3 months				
Elders	2											
Heath	24	1,480,000	35	1	¾ month		2			21	2–3 months	95
Huston	30			3	¼ month. All showed increased R.B.C.	58	13	1–4 months	70	14	1–4 months	85
Mason	1	1,500,000	40									
Minot and Murphy	105			2	8–12 months. One had associated sepsis		3	12 months		100	3 yrs. 11 months	87
Moore	7	2,250,000	49							6	6 months–3 yrs.	105
Ordway and Gorham	25			1	Died – pneumonia. R.B.C. rose over 1,000,000. 8 weeks over 1,000,000		1 / 1 / 3	18 months / Died – cystitis / 1–21 months	78	19	1–17 months / 3–21 months	
Panton and Valentine	20	1,100,000		1	½ month. R.B.C. rose over 1,000,000		6	½–3½ months	74	12	3½–16 months	
Poulton	2	1,630,000	30	1	5 months	55				2	2–3 months	94
Seyfarth	29	1,493,000		1	1 month					16	2–13 months	87
Sturgis, Isaacs, and Smith	50	1,500,000					12	¾–10 months	75	50	3½–13 months	
Starr	10	1,556,000	35							9	8–9 months	70
Thomson	5	1,120,000		1	7 days. R.B.C. rose over 1,000,000	42	1	14 months		3		
Vaughan	18	1,850,000	44	1	Died – cystitis	34	1	3 months		17	2–17 months	92
Weil, Pollet, Levy, and Flandrin	3	1,880,000								3	2–12 months	90
Total	395	Average	38	16	Average	44	54	Average	72	325	Average	89

That there must be some close relationship between the blood picture, glossitis, achlorhydria, and subacute combined degeneration of the cord is made evident by the striking fact that these four oddly associated lesions appear together in such apparently unrelated conditions as pernicious anaemia, sprue, and the so-called pernicious anaemia of pregnancy.

Table of Weights.

Pernicious Anaemia.

Case.	Before Treatment.			After Treatment.			Total Gain.			Time. Weeks.
	st.	lb.	ozs.	st.	lb.	ozs.	st.	lb.	ozs.	
1	9	2	6	12	0	0	2	11	10	56*
2	7	11	9	9	12	0	2	0	7	12
3	9	10	8	10	8	0	—	11	8	32
6	7	11	0	11	3	0	3	6	0	44
7	10	7	4	12	3	0	1	9	12	8
8	5	0	0	7	2	0	2	2	0	44
9	9	6	0	11	11	0	2	5	0	72
10	8	9	10	14	7	0	5	11	6	60
16	7	13	3	9	0	0	1	0	13	4
18	8	9	13	10	2	4	1	6	7	4

Secondary Anaemias.

Case.	Before Treatment.			After Treatment.			Total Gain.			Time. Weeks.
22	8	1	6	9	11	7	1	10	1	12
23	7	9	14	8	2	4	—	6	6	4
24	7	1	8	7	9	13	—	8	5	3
25	9	8	5	10	0	0	—	5	11	4

* In those cases treated over a long period the most marked increase in weight always occurred within the first six weeks of treatment.

Achlorhydria. In all cases in which a test meal has been repeated after some long period of treatment the achlorhydria has been found to persist, except in two. McPeak and Neighbors record a case of pernicious anaemia where free hydrochloric acid was found after treatment and not before. In the second case, described by Heeres, at the onset of treatment there was total achlorhydria, the red cell count was 920,000 and the haemoglobin 17 per cent. Nine months later, when the patient was seven months' pregnant, the red cells were 3,580,000 and the haemoglobin 52 per cent. A second test meal showed 25 per cent. of free hydrochloric acid in the gastric contents. Previous to the introduction of liver, Shaw had described one case where with a return to a normal count free hydrochloric acid had also reappeared. The patient remained well for three years. The recovery, therefore, of the power to secrete free hydrochloric acid would appear to be exceptional.

Subacute combined degeneration of the cord. The earlier reports as regards improvements in lesions affecting the nervous system were pessimistic, but it is clear that length of treatment is an important factor, and later reports have been more encouraging.

Ungley and Suzman have analysed a remarkable series of cases—thirty received liver, thirty-two did not. Of those receiving liver seventeen showed definite improvement. In this group there were only five deaths, all due to severe sepsis, while twenty-eight of those without liver died and none showed

any change for the better. In four cases the extensor response became flexor. In all numbness and tingling disappeared, leaving only a slight paraesthesia : muscle and joint sense was more or less completely recovered ; inco-ordination and ataxia diminished or was entirely lost : and the sphincter control was markedly improved. They conclude that the degree and rapidity of benefit is dependent upon the amount of liver taken, results being more certain and more rapid when treatment is begun at an early stage.

Minot and Murphy, in a series of one hundred and five cases, of which thirty-one had severe cord lesions, report only two that deteriorated. Isaacs, Sturgis, and Smith record three cases that developed neurological changes after the blood count had returned to normal.

Pal reports one case which showed marked improvement both in sphincter control and locomotion. Jensen and Fetter agree that early cord changes are much benefited. Bubert records a case where Rhombergism and ataxia were marked features of the condition ; after treatment neither were found, the knee-jerks had returned, together with improved sphincter control, and there was a change for the better in general mental outlook. Crouzon, Mathieu, and Gilbert-Dreyfus likewise report marked mental improvement in one of their cases who, previous to liver treatment, had been in an asylum with the mania of perse-cution. Their patient became normal in his mental attitude and recovered his power of locomotion, though the plantar responses remained extensor. Mason has reported an interesting case which had been treated for approximately four years. The red blood count returned to over 4,000,000 within two months of taking liver and has remained approximately steady. There was no improve-ment, however, in the nervous system until the fourth year, when the deep reflexes returned and all subjective symptoms were lost. The plantars still remained extensor.

It appears, therefore, that the length of treatment is an important factor as far as the central nervous system changes are concerned. A bad prognosis need not necessarily be given if there is no improvement coincident with the blood change. It is interesting to note that the knee-jerks appear to be more readily recovered than the ankle-jerks.

It is difficult to offer an explanation for this delay in the response of the nervous system. The ultimate lesion of subacute combined degeneration of the cord is as the name suggests an actual degeneration which one would imagine to be irrecoverable. If the lesions at first are due to toxaemia only it is difficult to understand why they should take so long to improve, especially when the associated anaemia responds rapidly. It raises the question whether the active liver principle may bear some specific relationship to the nervous system apart from its effect on blood formation.

The existence of cases with subacute combined degeneration, achlorhydria, no history of anaemia, and a normal blood picture, apart from a shift of the Price Jones curve to the right, lend some support to such a suggestion.

Glossitis. Glossitis was recognized by Addison as one of the cardinal signs

of his anaemia. Minot and Murphy claim that within a few months of treatment the tongue has usually lost its shiny appearance and become normal. Huston goes so far as to say that improvement in the circulation is readily discerned in the appearance of the tongue, though cases with true atrophy show no improvement in this respect. Heath, however, considers that actual regeneration of lingual papillae may occur. Isaacs, Sturgis, and Smith do not regard liver as entirely specific; they report a few cases in whom mild glossitis occurred during a remission. Starr mentions a case where glossitis recurred during a relapse due to insufficient liver intake. The count in this case fell to 3,400,000 only, but the glossitis was definite. This is of interest as showing the close association between the anaemia and the tongue condition, and explains why sore tongue may be one of the earliest symptoms complained of, occurring as it does before the anaemia is severe.

Group II. Anaemia associated with sprue and pregnancy.

In the second group are placed two conditions appearing widely different— sprue and the so-called anaemia of pregnancy, which both react in many cases as dramatically as true pernicious anaemia to liver therapy.

The relationship of both these conditions to Addison's anaemia has hitherto been obscure, but a consideration of their clinical response to liver and of their blood picture, together with certain experimental findings to be discussed later, suggests that the same underlying disturbance of the bone marrow, dependent, it may be, on different causes, is at times present in the three diseases.

The anaemia in sprue may be of two types, one an anaemia definitely of the secondary type, the other so closely simulating pernicious anaemia as to make differential diagnosis difficult.

The reports of treatment with liver are regrettably few; it is not mentioned by Weiss or Low in their recent reviews of the subject. Ashford has published a brief summary of his findings in twenty cases. In ten of these cases the anaemia was of the pernicious type, and these all responded well to treatment with liver extract, showing a typical reticulocyte shower in cases with a red cell count below 2,000,000. A case treated with monilia vaccine at the same time, but no liver, showed an increase in reticulocytes but no appreciable alteration in the red cell count. Those cases with the blood picture of a secondary anaemia showed no reticulocyte response, but details are not given of the total red cell count. Single cases that responded satisfactorily are quoted by Elders, Vaidya, and Panton and Valentine. In all these cases the improvement is far more dramatic than that claimed for any other line of treatment, and is similar in every respect to that found in pernicious anaemia.

The pernicious anaemia of pregnancy was first described by Channing in 1842. It is, in the majority of cases, indistinguishable from true Addison's anaemia, except by the important fact that it is curable. It is characterized by

severe anaemia, a high colour index, megalocytosis with the presence in many cases of nucleated red cells and megaloblasts, and may be associated with a sore tongue, achlorhydria, paraesthesia, and shooting pains.

These cases usually recover slowly on treatment with either blood transfusion, or iron and arsenic. Six out of the seven cases treated with liver, however, responded more rapidly.

Evans has recently described two interesting cases. The first case became anaemic in the latter half of her third pregnancy. Delivery was normal, and there was no excessive haemorrhage, but the pallor and weakness continued. When she was seen one month later her red cells were 1,200,000 and the haemoglobin 16 per cent., and the white cells 2,640. She was given ½ lb. fresh liver daily, with a resulting rapid rise in both haemoglobin and red cells, which remained normal when seen eight months later. In the second case, premature delivery of the fourth child was unaccompanied by excessive loss of blood. The patient was given liver and extract, but vomited both: on general treatment the red blood cells rose from 900,000 to 2,800,000 and the haemoglobin from 16 per cent. to 72 per cent. She was then given liver extract, which she tolerated well, and which appeared to accelerate the return of the blood count to normal.

Deschamps describes a case where the blood count rose from 1,800,000 to 5,000,000 after twenty-four days' treatment. Devraigne and Laennec report two cases, one of which was twice transfused and then died with a red cell count below 1,000,000. The second was treated with both transfusion and liver diet. The count rose rapidly from 1,890,000 and the haemoglobin from 45 per cent. to 75 per cent. The authors attribute the cure here to liver rather than to the transfusion, which had failed so noticeably in their first patient.

Vaidya further claims that eleven out of thirteen cases of anaemia of the pernicious type occurring in Indian women under his charge showed a marked improvement. It is clear from Balfour's statistical enquiry into pregnancy anaemia in India that it is a far more common disease, especially in the pernicious form, than here, but the fact that it is occasionally associated with complicating factors, such as syphilis or malaria, makes it difficult to accept Indian figures unless full details are given. Vaidya unfortunately gives us too little information to enable us to assess the value of his results.

Minot reports two cases who had apparently been somewhat anaemic for years; one had achlorhydria and one a slightly enlarged spleen. The blood picture did not altogether resemble that of pernicious anaemia though the colour index was in the neighbourhood of one. There was a rapid reticulocyte response to liver feeding followed by the return of the total count to normal. He also reports a case associated with sepsis which failed to respond. This is not surprising if we remember the important influence infections have upon the efficiency of liver therapy.

Group III.   Anaemia secondary to haemorrhage.

Jungmann had no success in cases of simple anaemia due to haemorrhage, while Weil, Pollett, Flandrin, and Levy claim satisfactory results in this type of anaemia.   Minot is dubious of the value of liver after experience with ten cases.   Dyke reports two cases following gastric haemorrhage, which showed some response to the extract, though not comparable to that obtained in cases of pernicious anaemia.   He also describes three cases following parturition—one of the latter had a colour index of 1·04, so should probably fall into Group II. Iron was given at the same time in some instances, and he considered that the best results are obtained by combining the two treatments.   The present writer has treated seven cases following gastric haemorrhage, four with excellent results, though only one showed any reticulocyte response.   Two cases following operation were unaffected, but as one was complicated by sepsis this is not surprising, and a third did well.   Equally good results were obtained with the extract as with whole liver.

It is clear, therefore, that though liver is not a specific agent in promoting blood formation in anaemias due to haemorrhage, it does, at least in certain cases, appear to be of real value, as one would have expected in view of Whipple's original experimental results on dogs rendered anaemic by repeated bleeding.

Group IV.   Anaemias secondary to other conditions.

(i) *Nutritional anaemia.*   Tuschener, after treating five children suffering from anaemia secondary to infection and alimentary disturbance, was struck with the definite improvement he obtained on feeding liver.   This, however, did not appear until the third or fourth week of treatment, emphasizing once again the importance of a prolonged trial of liver therapy.

Mackay found that whole liver was as effective as iron and ammonium citrate in infants, anaemic owing to deficient diet.   She believes this to be due to the iron content of the liver, since extract gave a negative or doubtful response in two cases after three weeks' trial, a period long enough to give a reaction to direct iron feeding.   Liver or liver extract did not appear to hasten the cure when coupled with iron medication nor to produce any summation of effect as it did in the experiments of the Wisconsin workers (Hart, Waddell).

The writer has had one case of a young man of 18 who was definitely under-nourished.   He had a severe secondary anaemia with no obvious cause, and responded extremely well to liver, his red cell count rising from 3,000,000 to 5,000,000 in a month and his haemoglobin from 40 per cent. to 70 per cent., while he gained over 9 lb. in weight.

(ii) *Leukaemia.*   Thomson reports a case of lymphatic leukaemia with intense aplastic anaemia subsequent to benzol treatment, which showed no improvement on liver diet given for three months, followed by extract for

two weeks. Weil, Pollet, Levy, and Flandrin claim definite improvement in leukaemias and splenic anaemia, but give no details. Minot treated six cases with no result, and two cases of aleukaemic myelosis, but some of these received only three weeks' treatment, which is not always, even in pernicious anaemia, a sufficiently long period. The writer has reported one case of aleukaemic lymphatic leukaemia which did not respond.

(iii) *Hodgkin's disease*. Minot treated one case for three weeks with no improvement in the total red cell count, though the reticulocytes rose on the eleventh day to 6 per cent.

Anaemia associated with splenomegaly. Fiessinger and Casteran describe a case of splenomegaly and anaemia of unknown origin of some years' duration associated with attacks of jaundice and indigestion whose red cells rose from 2,200,000 to 4,100,000 and her haemoglobin from 35 per cent. to 85 per cent. after four months' treatment with whole liver. The spleen was no longer palpable, and the patient was active and well, while before she had been so gravely ill that splenectomy was contemplated. Since the colour index was in this case originally below 0·8, it is improbable that she was a true pernicious anaemia.

(iv) *Splenic anaemia*. Minot treated one case before and after operation with no result.

(v) *Aplastic anaemia*. Dyke describes two cases of aplastic anaemia associated with epistaxis and bleeding from the gums, one of which died after two weeks' treatment and the other after a month. Minot failed to note any improvement in one case of aplastic anaemia. Hayes Smith has recorded one case of so-called aplastic anaemia that reacted well to a liver extract. The question what constitutes a true aplastic anaemia is too controversial to be entered into here, but in this case the diagnosis is perhaps open to doubt, since on no occasion was the haemoglobin percentage below 58, and the lowest total white count recorded was 3,970. The case was simultaneously treated with vaccines, Haemostyl, Bemax, Ostelin, &c., so it is hardly fair to claim that improvement was due to the liver extract.

(vi) *Acholuric jaundice*. Panton and Valentine describe one severe case of acholuric family jaundice which did not respond to whole liver after ten days. This is a short period on which to place a negative conclusion, and the fact that the reticulocyte count rose from 45 per cent. to 65 per cent. is of no importance, since it is always a fluctuating figure in this disease.

Minot reports a case which he states resembled chronic acquired haemolytic icterus with a reticulocyte count of 200,000 per cm., which decreased rapidly as the red cell count rose to normal. This is surprising in view of what we know of this condition.

(vii) *Haemolytic anaemia*. Marchiafava discusses two cases of haemolytic anaemia characterized by haemosiduria and of unknown aetiology treated with whole liver for two months without effect.

The writer had one case of severe unexplained haemolytic anaemia with

a high colour index and an absence of hydrochloric acid, but with a negative Price Jones curve, who failed to respond to liver after three weeks' trial.

(viii) *Nephritis*. The association of anaemia with chronic nephritis has long been recognized but not explained. The fact that kidney is as effective as liver in treating pernicious anaemia raises many interesting speculations on the possible connexion of deficient renal tissue and faulty blood production. Thomson found no improvement on treating one such case with whole liver. Davidson reports a case in which the reticulocytes rose to 15 per cent. on the twelfth day, but gave no further information.

(ix) *Tuberculosis*. Both Dyke and Thomson report failure in cases of tubercle associated with anaemia.

(x) *Certain toxic and infective anaemias*. Middleton reports favourable results in toxic cases following Cohn's extract, but gives no details. Coates and Delicati followed a series of cases of anaemia associated with infective arthritis treated either with extract or whole liver, and claim that nine out of twelve cases were definitely benefited. They give full figures, but their results are not convincing, as in no case was the anaemia severe. The most satisfactory response was a rise in red cells from 3,230,000 to 5,700,000 and of haemoglobin 60 per cent. to 62 per cent. Those cases that improved showed an increase in the polymorphonuclear count as contrasted with those that were unaffected.

Minot describes two cases of sepsis and one of infective endocarditis that were influenced by liver therapy.

(xi) *Anaemia associated with syphilis*. Fournier first described rare cases of so-called pernicious anaemia with associated syphilis. Foucar and Stokes, in reporting 4,800 cases of syphilis, found only twenty-five with such an anaemia, and in view of its close clinical similarity to pernicious anaemia it is open to doubt as to whether it is not rather true Addison's anaemia occurring in a patient with a syphilitic infection rather than an anaemia secondary to such an infection. This doubt is increased by three such cases recently reported by Maurer, Richter, and Koessler, all of which responded to liver therapy. These cases all had nervous signs compatible with subacute combined degeneration of the cord, achlorhydria, glossitis, and slight icterus. In two the Wassermann reaction was positive, while the third was negative, but the patient gave a history of a chancre some years previously, and showed on examination serpiginous ulcers on the arm which were thought to be syphilitic. In all cases the response to liver therapy was satisfactory after general treatment had failed.

The present writer had one case of a slight degree of anaemia associated with syphilitic spastic paraplegia, who showed no response after a fortnight's treatment.

(xii) *Secondary anaemia of unknown causation*. Minot describes three cases with no obvious cause for the anaemia. In one the red blood count was reduced by more than 50 per cent. below normal. Bone marrow obtained at biopsy was like that of pernicious anaemia, but the icteric index was normal and there was no glossitis, central nervous system lesion, or achlorhydria. The

second case had a three years' history. The blood picture resembled that of a secondary anaemia, the size of the red cells being normal when the count was below 2,000,000. The third had a colour index approaching one, but the blood picture was not pernicious in character. She had lesions on her hands simulating pellagra. Achlorhydria was present. On receiving liver her reticulocytes rose to 11 per cent. All three cases reacted well to liver therapy.

The present writer had one case of unexplained anaemia who improved. Her red cell count rose from 4,600,000 to 5,800,000 and her haemoglobin from 37 per cent. to 56 per cent.; a second somewhat similar case showed no response.

A case of lymphosarcoma, which was originally diagnosed and reported as one of pernicious anaemia, did extremely well. When first seen the patient had a secondary anaemia associated with diarrhoea. A year later his blood count and appearance seemed to justify a diagnosis of Addison's anaemia, though the Price Jones curve showed no appreciable increased variability and only a slight shift to the right—the mean diameter being $7.8595\,\mu$. The red cell count and haemoglobin percentage responded rapidly to liver though he never gained in weight or improved in general health. A few months later he was found, at operation, to have widespread lymphosarcomatous deposits. It is possible to argue that the lymphosarcoma was imposed on the pernicious anaemia, but the atypical Price Jones curve makes it more probable that in this instance there was a response to liver therapy in some condition other than pernicious anaemia, and emphasizes once again the importance of giving liver a fair trial in obscure cases of disturbed blood formation in which the diagnosis is uncertain.

Minot reports no success in single cases of the following: cirrhosis of the liver, colitis, chronic chlorosis with achylia gastrica, multiple myeloma, cancer, and lymphoblastoma.

Discussion.

In May, 1919, 1929 Cohn, Minot, Allies, and Salter published full details of the method used to obtain an extract of the active liver principle, and as a result of analysis they considered it to be a nitrogenous base or polypeptide, of which about 0·6 grams a day had been sufficient to produce a pronounced reticulocyte response in a patient with pernicious anaemia.

Recent experimental work suggests that there are probably many factors in liver which affect blood formation, and, further, that some of these factors are present in other foods. Whipple showed in his original paper, in 1925, that kidney was as effective as whole liver in increasing haemoglobin production in his dogs rendered anaemic by bleeding. Minot reports as satisfactory results in the use of kidney as of liver in treating pernicious anaemia.

Factors concerned in normal blood production, The question as to the nature of the factors concerned in normal blood production has been attacked in two rather different ways:—

(i) Whipple and his associates and the Wisconsin group (Hart, Waddell) have carried out feeding experiments with reference to haemoglobin formation.

(ii) Peabody and Muller have studied the effect of feeding various liver fractions on the bone marrow.

Careful analysis of the majority of common foodstuffs by Whipple and his associates and the Wisconsin school has given rather conflicting results. This is perhaps due to the fact that one group worked with dogs rendered anaemic by bleeding, the other with rats anaemic due to deficient nutrition. Both agree, however, that the mineral salt content is an important factor, more especially the iron and copper balance. They agree in finding some summation of effect between these two salts, and the Wisconsin school claim that copper alone is effective when iron has failed. They also found the Eli Lilly extract potent, while Whipple thought it valueless.

Mackay's finding already discussed, that whole liver is effective in the nutritional anaemias of infants while extract is not, is difficult, however, to explain.

Unfortunately neither Whipple and his associates, nor the Wisconsin school, make any mention of the appearance of the bone marrow of their animals which should be of considerable interest. It is clear, however, that other mineral salts besides iron play an important part in haemoglobin formation.

Peabody and Muller have attacked the problem from a different angle. Peabody's recent studies of bone marrow in pernicious anaemia have shown us that the characteristic picture is of intense proliferation of megaloblasts. The marrow is packed with these primitive cells showing few nucleated or normal red cells. On feeding liver the character of the bone marrow changes, the megaloblasts being replaced by nucleated and mature red cells, so that ultimately a completely normal appearance is regained. This change accompanies the return to a normal blood count.

Muller analysed the effect of feeding liver and other substances on blood regeneration, as evidenced by the changes produced in pigeons whose bone marrow was rendered aplastic by starvation.

She claims to have demonstrated two factors in liver affecting blood production.

(i) A substance favouring normal blood production.

(ii) A substance which inhibits the division of the primitive red cell, the megaloblast.

She found on feeding pigeons with whole liver that there was at first a gain in weight associated with megaloblastic hyperplasia of the bone marrow, and both the red cell count and haemoglobin rose to a point just below normal, followed by a fall to a position just above the original anaemic level. The bone marrow, however, showed a definite suppression of megaloblastic formation. A similar result was obtained by feeding alcohol-treated liver. If, however, the residue after alcoholic extraction was given there was a considerable replacement of weight, red cells, and haemoglobin, though a completely normal level

was never reached. She concludes that the anaemia following whole liver is due to the success of some inhibitory substance rather than to the lack of stimulating factors.

This is in agreement with Heaton's finding while working with tissue cultures that liver contains two substances affecting the growth of fibroblasts, one growth promoting, one growth inhibitory.

Mode of action of active liver principle. It is clear, then, from both Peabody and Muller's work that liver contains some substance affecting particularly the development of the megaloblast. We should, therefore, on *a priori* grounds expect liver feeding to exert a powerful action on those forms of anaemia due to disordered production of megaloblasts by the bone marrow.

What evidence have we then of megaloblastic hyperplasia associated with anaemia in clinical conditions? As already mentioned, Peabody has shown a hyperplasia to be the characteristic picture of the bone marrow of pernicious anaemia. The blood picture in sprue and the anaemias of pregnancy are so similar to that of pernicious anaemia that they are often indistinguishable. Hampson and Shackle record twelve consecutive cases of sprue that gave a typical Price Jones curve, and Baumgartner and Smith return two cases that on measurement showed many large cells well over $8\,\mu$. More recently Fairley, Mackie, and Billimoria have analysed sixty-seven cases, attempting to correlate the blood findings with those of the bone marrow. The average colour index was 1·0. A Price Jones curve was made in eleven cases: in all it was typical of the pernicious form, showing marked anisocytosis with definite increase in the mean diameter—'essentially the anaemia is of megalocytic type'. Examination of the bone marrow in some cases showed two that were indistinguishable from that of pernicious anaemia; one had mild hyperplasia and the remaining five were aplastic with islands of hyperplasia. The latter cases showed a typical Price Jones curve, and the authors, therefore, conclude that these small hyperplastic areas are responsible for the megalocytosis, that the anaemia is essentially of megaloblastic type and dependent upon a deficient blood production rather than blood loss.

Hampson and Shackle found a Price Jones curve typical of pernicious anaemia in one case of pregnancy anaemia they investigated, and all authors emphasize the fact that large cells are a striking feature of the blood picture.

The post-mortem records are, however, scanty in the cases associated with pregnancy and give no detailed account of the bone marrow histology.

Esch in his review of the subject records two cases, one of which gave a typical history and blood picture of the pernicious type, in the other the colour index was low, 0·5. The post-mortem findings in both were similar to those in true pernicious anaemia. Neale describes one case with soreness of the tongue and macrocytosis in the blood, though the colour index was only 0·7, which he considered fell into this group since the bone marrow was found *post mortem* to be hyperplastic. Balfour, in her series of 150 cases among Indian women, in which the average colour index was 1·4, only records two autopsies. Both

showed free iron in the liver and spleen. Areas of bone marrow were aplastic, but in one large numbers of megaloblastic cells were seen and in the other ' active normal marrow cells with mitosis '.

The fact that the only three conditions in which the Price Jones curve is shifted to the right and in which there is evidence of megaloblastic hypertrophy of the bone marrow are the three which respond in a characteristic way to liver suggests that the underlying disturbance is the same, i. e. a domination of the megaloblast.

Muller considers that the underlying pathology of pernicious anaemia is an over-stimulation of the reticulo-endothelial system characterized by an excessive production of megaloblasts, increased blood destruction, and bilirubin formation. On feeding liver the inhibitory factor comes into action, causing a cessation of megaloblastic formation, giving those present an opportunity to mature in a normal manner because excessively rapid cell division, capable only of producing more megaloblasts, has been suppressed. Liver acts, therefore, in her opinion, by inhibiting the production of megaloblasts.

Peabody and Minot interpret the effect of liver in a rather different manner. They consider that in pernicious anaemia liver provides a substance necessary for the maturation of the megaloblast. The megaloblasts, owing to lack of some substance, are unable to develop, and, therefore, unable to utilize the pigment present from the normal breakdown of red cells. This accumulates in the serum, giving a positive van den Bergh reaction, and increases the output of urobilin. The jaundice, therefore, of pernicious anaemia is due to deficient utilization of pigment rather than excessive destruction, the anaemia to deficient production of red cells rather than to massive destruction.

The point at issue between these two hypotheses is whether the active principle exerts its action by inhibiting the production of megaloblasts or by stimulating their maturation.

We have at present only a brief note on Sabin's observation that the addition of extract to the culture medium of chick embryos causes increased rapidity of cell division. She does not make it clear whether this involved maturation or was only simple division, which in view of Muller's hypothesis becomes increasingly important. Minot's observation on the effect of extract on both the staining and metabolism of reticulated cells perhaps favours the idea that something more complicated than mere cell division is involved.

Muller has not attempted any explanation of the effect of liver on the experimental anaemias of Whipple and the Wisconsin school along the lines of her hypothesis for the aetiology of pernicious anaemia. She produced her anaemia by complete starvation ; the Wisconsin school by deficient diet. The two are, therefore, perhaps not directly comparable, and until we know more of the bone-marrow picture in the Wisconsin rats no conclusion can be drawn. It is rather surprising, however, that if the inhibitory substance in liver is as potent as she claims, it should never have shown its inhibitory action on any part of the delicate mechanism of the reticulo-endothelial system in those

animals with definite nutritional deficiency. She also does not explain why that fraction of liver thought to contain the growth-stimulating factor only is unable to raise the red-cell count and the haemoglobin to a normal level, which is a point of some difficulty.

Minot's suggestion that liver exerts its action in pernicious anaemia by stimulating maturation of the megaloblasts though with no exact experimental evidence behind it, has on the other hand little evidence against it, and it is not in conflict in any way with the work of Whipple and the Wisconsin school. He finds that if patients are treated with liver extract and a diet poor in those substances which Whipple has shown to promote haemoglobin formation in his dogs rendered anaemic by repeated bleeding, that the haemoglobin rises less rapidly or not at all after an initial period than in those receiving whole liver or a well-balanced diet. He suggests, therefore, that ' there are other substances in liver, among them iron, which facilitate haemoglobin formation. The lack of these substances may become evident after some weeks of treatment when the critical stages of the disease are past and the specific substance deficient in pernicious anaemia and not obtained by the patient from his tissues or his food has been supplied '. It is possibly these substances which are responsible in part for the effects obtained by Whipple, though he found, as already stated, that liver quite apart from its salt content exerted some specific effect on haemoglobin formation in his dogs.

Nature of the deficiency in pernicious anaemia. An interesting hypothesis has recently been put forward by Castle as to the cause of the deficiency present in pernicious anaemia. He suggests that owing to the lack of gastric secretion the body is unable to prepare some protein substance essential for proper blood production. This substance is normally stored, perhaps having been further elaborated, in liver or kidney, and therefore when liver is fed to a patient with pernicious anaemia the requisite protein is supplied and normal blood production restored. In support of this hypothesis he found that whereas gastric juice did not have any effect on blood production the stomach contents removed from a normal person 45 minutes after a meal of beef muscle, which is alone valueless as a stimulus to blood production, produced a typical reticulocyte response when fed to a patient with pernicious anaemia. This observation was successfully repeated in eight cases. Digestion of the beef muscle *in vitro* was unsuccessful, so he concludes that some enzyme, other than commercial pepsin, working in an acid medium and at present not isolated, is essential, and that the absence of such an enzyme is associated usually with an absence of free hydrochloric acid.

If the original hypothesis is correct it is difficult to understand why a small proportion of healthy normal people have complete achlorhydria and no pernicious anaemia, and why so many cases of severe secondary anaemia also show a complete absence of hydrochloric acid. There are also a few undoubted cases of true pernicious anaemia who have apparently normal gastric secretion. Such cases though inconvenient cannot be disregarded.

The finding of a megalocytic type of anaemia in sprue which reacts well to liver might be explained in view of Castle's hypothesis by the fact that the diseased intestinal wall is unable to absorb the first stage of the breakdown product formed by the action of some enzyme present in the stomach on the protein of the food. When the finished substance as stored in the liver is fed this is however more readily absorbed.

It does not appear possible at the present time to offer any complete explanation of the part played by liver in blood formation, but it is clear both from clinical and experimental findings that its action is a complex one dependent upon several factors, one or more of which may be effective in various conditions.

We can distinguish the part played by the inorganic salt content of the organ especially in the nutritional anaemias and the part played by the so-called active principle in those anaemias characterized by megaloblastic hypertrophy and megalocytosis—pernicious anaemia, sprue, and the anaemia of pregnancy—where the supply of such small quantities of an unknown substance appears to affect so many lesions as do vitamins in the deficiency diseases. The relative importance of these two groups, the inorganic salts and the active principle which is probably a complex body, in other anaemias such as those secondary to haemorrhage either experimental or clinical where both doubtless play their part is at the moment impossible to assess.

Our understanding of the exact aetiology of anaemia is perhaps little further than it was four years ago, but we are certainly in possession of a new and powerful therapeutic agent and of much fresh knowledge concerning the factors necessary for blood production.

Conclusions.

1. Liver is a certain remedy in those forms of anaemia characterized by megaloblastic hyperplasia of the bone marrow, i.e. (a) pernicious anaemia; (b) sprue; (c) the pernicious anaemia of pregnancy.

2. The therapeutic action of liver is seriously inhibited by the presence of sepsis.

3. Liver is of definite value in some cases of anaemia secondary to gastric haemorrhage and in the nutritional anaemias.

4. Liver appears without value in other forms of anaemia.

5. The action of liver is dependent upon at least two distinct factors: (a) its inorganic salt content; (b) the complex polypeptide isolated by Cohn, Minot, Allies, and Salter, one or both of which may be effective in varying conditions.

6. Pernicious anaemia must be recognized as a deficiency disease. In the absence of some principle present in liver and kidney the bone marrow is unable to produce its normal quota of red cells, and anaemia, therefore, ensues.

This substance is probably lacking, though from other causes, in sprue and the anaemia of pregnancy.

7. The severe nervous lesions of subacute combined degeneration of the cord may improve considerably long after a normal blood picture has been achieved if treatment is continued.

8. In patients suffering from pernicious anaemia sudden improvement in mental outlook and a rapid gain in weight are characteristic and as important a sign of a satisfactory response to liver treatment as a rise in the reticulocyte count.

9. The leucopenia of pernicious anaemia is not invariably lost as a result of liver treatment.

10. The claim that an eosinophilia is characteristic of the response to liver appears to be without satisfactory foundation.

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OBSERVATIONS ON THE AETIOLOGICAL CORRESPON-DENCE BETWEEN ANGINAL PAIN AND CARDIAC INFARCTION [1]

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In the past few years many observers have recorded their experiences of a syndrome sometimes described as that of coronary thrombosis, more accurately, perhaps, as that of cardiac infarction, or ischaemic necrosis of the cardiac wall. Not the least interesting and valuable outcome of these observations has been the light that they have thrown on that obscure matter, the origin of anginal pain. It is true that a severe and even fatal infarction may cause no pain (East, Bain, and Cary (1)) but this is exceptional. Usually the prominent symptom is an oppressive or ' tight' sensation, varying from a sense of pressure to an intense and intolerable pain, referred to the sternal region, sometimes to the manubrium, sometimes to the ensiform cartilage, sometimes in between. These sensations have so much in common with those of the anginal attack that is excited by exertion and relieved by repose that they are usually assumed to be different grades of the same process. If this is indeed true, then we have good reason for belief in the coronary theory of angina. The relationship is, however, not quite as clear as this, for not more than one-third of the patients who develop coronary thrombosis have had previous experience of cardiac pain ; and it is only a minority of those who suffer from anginal attacks in whom thrombosis ultimately develops. The object of the analysis recorded here is to discover how far the two syndromes, that of cardiac infarction on the one hand and that of the angina of effort on the other, are aetiologically related. In other words, do both kinds of attack occur in the same kind of patient ? To this end, the histories given by a series of patients were scrutinized, and two groups were formed, the first consisting of those in whom a diagnosis of cardiac infarction had been made, and the second of patients suffering from the angina of effort. The first group consisted of cases in which cardiac pain, persistent in character, and not necessarily excited by effort, was followed by evidence of gross injury to the wall of the heart ; the second, of cases in which the pain was excited by effort, relieved by its cessation, and not followed by structural sequelae. In the first group (taken from notes of private practice) were 86 cases, in the second 201.

The first method of comparison applied to these two groups of cases was that of determining the *age* incidence. The result is set out in Table I.

TABLE I.

Angina of Effort.		Cardiac Infarction.
Age	%	%
21–30	2·0	0·0
31–40	3·0	3·5
41–50	9·5	8·1
51–60	31·0	19·8
61–70	38·0	52·3
71–80	15·5	12·8
81–90	1·0	3·5

It is seen that there is a close correspondence between these two sets of figures. The incidence of the effort angina is, it is true, heavier in the sixth decade than that of the graver syndrome. This is partly explained by the fact—brought out clearly in a later table—that cardio-aortic syphilis, which spares few of its victims to the age of sixty, is often associated with the angina of effort but rarely with cardiac infarction.

The *familial* incidence of angina pectoris is well known. It is not difficult to recall striking examples. For example, I know of one family where the father and four children all suffered from pain of the coronary type. One of them died suddenly at a comparatively early age, and another developed symptoms which were without doubt those of cardiac infarction some months before his death, which also was sudden. In the present series of cases diagnosed as 'cardiac infarction' there were two pairs of near relatives. One of these pairs consisted of father and son. (Since writing this I have seen a man whose father died of unmistakable coronary thrombosis. The son, after a series of attacks of cardiac pain, shows the electrocardiographic changes characteristic of coronary occlusion.) There are two possible interpretations of this familial incidence. One is that it is nothing more than an example of the well-known liability of certain families to arterial degeneration, a liability which is apt to be particular as well as general since it includes a predilection for certain vessels. For example, there are families whose members all die of cerebral haemorrhage. Another suggestion is that aberrations of the coronary arteries which, as Hadfield (2) has pointed out, may throw an undue measure of responsibility on the one trunk, may run in families.

Perhaps the most interesting and enlightening of all the figures extracted from this analysis are those which display the incidence of these two syndromes in relation to *aetiology*. The following table expresses, in percentage form the liability of the various aetiological groups to the angina of effort on the one hand and to cardiac infarction on the other.

This table serves to illustrate the fact that the three great infective diseases of the heart—cardiac rheumatism, ulcerative endocarditis, and cardiac syphilis —seldom excite the coronary syndromes. To this general statement there is one interesting and significant exception. Pain of the kind that characterizes

ischaemia cordis was experienced by nearly half my cases of cardio-aortic syphilis. In a few others, the character and behaviour of the pain were not typical, and these have been excluded from the ischaemial category. The calculation of the incidence of pain excited by effort in cardiac syphilis is therefore on the low side. Yet cardiac infarction is rarely seen in cardiac syphilis, only once in fact in 88 cases. This, I believe, agrees with the experience of other observers.

TABLE II.

	Total Cases.	Percentage experiencing cardiac pain without sequential changes of structure.	Percentage in which cardiac pain, followed by gross change of structure, occurred.
Congenital malformation of heart	35	5·7	0
Rheumatic heart disease	579	6·4	0
Progressive bacterial endocarditis	102	6·8	0·9
Cardio-aortic syphilis	88	43·2	1·1
Thyrotoxic heart disease	89	6·7	0
Alcoholic heart disease	27	3·6	0
High arterial tension	293	16·3	4·1
Senile degeneration of the heart	377	29·2	15·1

The freedom of those attacked by rheumatic infection of the heart from symptoms of coronary disease is probably more complete even than these figures represent. In some instances where the patient complains of pain and oppression under the sternum it is due to pericarditis; in others, the mere fact that the heart is enlarged seems to cause discomfort which, increased by exertion, may simulate the ischaemic syndrome. The only case of active rheumatic carditis exhibiting that syndrome in a characteristic and unmistakable form that has come under my observation during the past ten years, i. e. the only one in a series of some hundreds of cases, is that reported by C. B. Perry (3). It is also the best example of coronary arteritis in rheumatic heart disease that I have examined histologically. Among the cases of rheumatic heart disease analysed here there was not a single instance of cardiac infarction.

The fact that in a series of more than a hundred cases of ulcerative endocarditis there was only one in which there were symptoms suggestive of coronary embolism is as remarkable as the absence of such symptoms from rheumatic heart disease. Microscopical examination of the cardiac muscle in ulcerative endocarditis nearly always discloses some evidence of infarction, recent or old. Usually, it is true, these infarcts have been caused by emboli plugging the smallest arterioles; but one would expect now and again to come across an infarction of the heart wall gross enough to declare itself in some drama symptomatic of myocardial necrosis.

The possibility of a relation between sepsis and angina has recently been suggested by Neild (4) in a paper describing two cases that may be construed as illustrating this relation.

In several cases apparently belonging to the category of cardiac infarction, occurring in young middle-aged patients, a phlebitis has preceded the onset of

the cardiac attack, but in the case I am about to describe the phlebitis followed it. A professional man of forty with an excellent record of health injured his leg, fracturing the fibula though without displacement, early in January. As this was recovering, in the middle of February, he was seized with pain in the chest, slight fever, and a transient haemoptysis. This cleared up, but about ten days later he became suddenly ill and a gangrenous appendix was removed. About a fortnight after his operation, he felt a sudden sense of oppression in his chest as if something had given away, and he became faint. The next day his temperature had risen to 100·8, his pulse-rate to 120, he looked grey and distressed, and a pericardial rub was audible over the lower sternum. That night this had gone, and next day he was better, but it is interesting to note that even then he had the narrow pulse pressure—105 systolic and 80 diastolic—that is so often seen in coronary infarction. A week later he had entirely recovered from this attack, but a severe thrombophlebitis extending down from the left groin had set in. Eventually he got rid of this, and an electrocardiogram taken on May 18 showed no gross abnormality. It is difficult to interpret in detail this sequence of events, but the cardiac chapter is as suggestive of coronary thrombosis as the whole story is of some infective process. All the five or six patients whom I have seen in this kind of attack have made good recoveries, which is perhaps due to the fact that the oldest of them was 51. Possibly, also, these attacks are due to a venous thrombosis, less disastrous in its mechanical effect on the circulation through the walls of the heart than an arterial obstruction is. Similar events are also included in the series of phenomena entitled by Gillman Moorhead 'thrombophlebitis migrans' (5).

These interesting exceptions to the general rule, that infections of the cardiac muscle are not attended by pain of the cardiac type, do but prove the rule after all, for they are examples of infections, not of the cardiac muscle itself, but of the coronary apparatus. In confirmation of this belief, that the action of infective poison on the muscle of the heart does not itself cause cardiac pain, we may glance at the figures illustrating the rarity of cardiac pain in the thyrotoxic and alcoholic types of heart disease. In both groups the causal agent is presumably a chemical substance acting harmfully on the wall of the heart, probably on the myocardial cells. In neither is the incidence of cardiac pain, whether of the ischaemic or of the infarctive type, more than trivial. The inference, that toxic degeneration of the muscle-cells of the heart is not accompanied by or provocative of cardiac pain, is borne out by a consideration of the rarity of these syndromes in such infections as diphtheria, enteric fever, and malaria. In all these, and in others like them, the cells of the cardiac wall are invariably damaged; yet pain of the cardiac type rarely ensues.

It is important to establish this fact as it contrasts significantly with the next: the occurrence of cardiac pain in pernicious anaemia. In my own notes (6) of 36 cases of pernicious anaemia, substernal pain of the cardiac type was mentioned 8 times. This gives a very high percentage, much higher than in Willius and Giffin's experience (7). Probably it is too high, but at all events

it is true that in my experience substernal pain of the cardiac type is much more often excited by severe anaemia than by toxaemia. Further, Willius and Giffin have shown that we cannot ascribe the occurrence of this kind of pain in pernicious anaemia to the coincidence of coronary lesions, for post-mortem examinations proved the absence of these. It is to be presumed that the anaemia itself was responsible. Probably anaemia has this action by virtue of the anoxaemia of which it is the instrument, as Keefer and Resnik (8) have suggested. At all events it is apparently true that when the supply of oxygen carried to the heart wall is short, then pain of a cardiac kind may be experienced.

Let us now see how this last idea can be applied to the elucidation of the high incidence of the anginal syndrome in the syphilitic, senile, and hyperpietic groups.

The oxygen supply of a tissue may be rendered deficient by anything that diminishes the influx of blood into that tissue. Now, the flow of blood into the wall of the heart is unlike that into any other organ, in that it must chiefly take place during diastole. When the heart is in systole, its muscular wall is firmly contracted, and this contraction favours the emptying but opposes the filling of the coronary system (Anrep and others (9)). Conversely, it is when the wall of the heart is relaxed in diastole that blood can pass into the coronary arteries and forward into the capillaries with which the cardiac muscle is so richly supplied. The source from which this diastolic supply is derived is the first part of the aorta, immediately above the semilunar valves. At this point the blood contained in the aorta during diastole is being forwarded to the branches of the arterial tree by the elastic recoil of the thoracic aorta. This is rendered effective in one direction only—towards the periphery—by closure of the aortic semilunar valves. There are, therefore, three structures concerned in the supply of arterial blood to the wall of the heart: the first part of the aorta, the aortic semilunar valves, and the coronary arteries. If this apparatus is to work satisfactorily, the aorta must be elastic, the semilunar valves competent, and the coronary arteries both pervious and distensible.

Now, it is in the three kinds of heart disease named—the senile, the hyperpietic, and the syphilitic kinds—that this apparatus is most often damaged. Sometimes one part suffers most, sometimes another. For example, the syphilitic process affects both the wall of the aorta and also the orifices of the coronary arteries, and yet spares those arteries in their further course. The arteriosclerosis of old age, on the one hand, sometimes injures the course of the coronary arteries, sometimes the wall of the aorta, sometimes both. In both, again, the semilunar valves may be injured, or they may escape injury. Competency of the aortic valves is the least essential requisite of this apparatus for supplying blood to the cardiac wall; for in the rheumatic type of aortic incompetence, where the valves are damaged much, and the aorta and coronary vessels but little, angina is very rare, while in the syphilitic and atheromatous types of incompetence, where the valves are damaged but little, pain is common.

There can be little doubt as to the importance of the aorta on the one hand, and the coronary vessels on the other, in the causation of the ischaemic syndrome. What has been in doubt is the relative responsibility of these two sets of lesions for the provocation of the anginal attack. Clifford Allbutt put it down to the aortic account, but many observers have held to the belief that the coronary lesions were most to blame. If we accept the view that there is an apparatus for furnishing blood to the heart, of which an elastic aorta and distensible coronary arteries are essential parts, we shall incline to believe that there is no real rivalry between the aortic and the coronary hypotheses of angina. In some cases it is the fault of one part of the heart-feeding apparatus; in other cases it is the other part that is to blame; in others, again, both parts are so damaged as to be inefficient.

Too much stress has, perhaps, been laid on the mechanical aspect of the matter, and too little on its vitalistic side. This is particularly true of the coronary arteries. Sometimes these are laid open on the autopsy table, and because there is no obvious change of the intima it is assumed that the vessel is normal. But the media is after all the most important part of the arterial wall, and the efficiency of an artery is as dependent on the state of its middle coat as that of a heart is on the state of its muscular wall. Even when the coronary arteries are extensively calcified, we must not forget that this calcification spells rigidity as well as stenosis; and the one is at least as important as the other. A coronary artery, to answer to the rapid changes that are demanded of it, must be capable of distension at one moment and of elastic recoil at the next.

This is not to deny the part played by roughening of the arterial linings and narrowing of their channels in the production of cardiac infarction. How else are we to explain that startling discrepancy between the effects of arteriosclerosis and those of syphilis? Both cause ischaemic symptoms very often; but whereas arteriosclerosis not uncommonly causes infarction, syphilis causes it very rarely indeed. The obvious explanation is that arteriosclerosis usually roughens the wall and encroaches on the lumen of the coronary vessels throughout their course, while syphilis scarcely ever attacks these vessels except at their orifices. It does not alter the arterial linings in such a way as to prepare them for the formation of thrombi. That is why cardiac infarction is so rare in cardiac syphilis, so much rarer than it is in the decrescent type of cardiosclerosis.

If, in conclusion, we are invited to express a judgement against one or the other, the aorta on the one hand or the coronary arteries on the other, as the principal offender in provoking the anginal attack, we shall find evidence persuading us to accuse the coronary arteries. In the first place, we may consider that extreme degeneration of the abdominal aorta which is by no means rare. Professor Hadfield, while pathologist to the Bristol General Hospital, collected a remarkable series of specimens exhibiting these changes; yet only one of the patients from whom these were taken seems to have shown any clinical evidence of cardiovascular disease, and that was a woman who died of cardiac infarction.

If the elastic recoil of the aorta were of such immediate value to the tissues which receive their blood through the branches issuing from the diseased part we should expect such syndromes as that of intermittent limp to be much commoner than they are.

Again, lesions of the aorta, whether specific or not, are usually encountered in acute rheumatic carditis; yet it is not until severe coronary lesions are added to these that pain of an anginal kind is provoked.

Finally, there is the evidence gained by Gross (10), Campbell (11), and others, using injection methods to demonstrate changes in the coronary circulation. By this means it is seen that as age advances two changes proceed side by side: encroachments on the lumen of the main coronary vessels on the one hand and increase in the vascularity of the subpericardial fat on the other. It is difficult not to conclude from this that serious reduction in the effectiveness of the coronary circulation imposes on the cardiac muscle an urgent need for the creation of anastomotic channels by which the diastolic flush of blood may be received in spite of obstruction in the principal trunks. The progress of these changes, decade by decade, agrees so closely with the increasing incidence of anginal attacks, decade by decade, that it seems justifiable to regard them as closely related facts.

Summary.

1. The aetiology of two groups of cases, one of the angina of effort, the other of cardiac infarction, is compared.

2. The age and sex incidence of the two groups corresponds closely with one another.

3. The angina of effort occurs principally in association with cardiac syphilis, high arterial tension, and senile degeneration of the heart.

4. Cardiac infarction occurred in the second and third of these three aetiological groups but rarely in the first.

5. Both syndromes are rare in the other infective and toxic diseases of the heart.

6. The occurrence of cardiac pain in pernicious anaemia is alluded to.

7. It is concluded that pain of an anginal kind is produced by those types of disease which fail to forward oxygenated blood to the cardiac muscle.

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THE MAIN BRANCHES OF THE CORONARY ARTERIES IN ACUTE RHEUMATIC CARDITIS [1]

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With Plates 11 to 14

WHILE many workers, Romberg (1), Cowan (2), Coombs (3), and others have described lesions of the smaller branches of the coronary circulation, few observers seem to have paid attention to the condition of the main divisions, such as the circumflex and anterior and posterior descending branches. Rabé (4) described a case in which the coronary arteries showed both an endarteritis and a mesarteritis; the former characterized by an amorphous irregular thickening of the intima, and the latter by disintegration of protoplasm and vacuolization of the fibres—'l'êtat réticulaire ou alvéolaire de la tunique moyenne'. He argues from this that acute rheumatism may be an important aetiological factor in the production of arteriosclerosis. Klotz (5) stated that in acute rheumatism the main coronary arteries were little affected, except at the periphery of the adventitia, which in some cases showed an inflammatory infiltration which progressed to a perivascular fibrosis.

Pappenheimer and von Glahn (6) have described an 'unusual' cardio-vascular lesion in rheumatic fever with panarteritis of the larger arteries (coronaries, renal, superior mesenteric, and coeliac axis) in two cases. In this change the intima is thickened by the new formation of a loose fibrocellular material, which is in some places cellular, while in other places the cells are few and far apart, being separated by a pink hyalinized ground-substance. The internal elastic lamina is irregular and split up. The media shows scattered polymorpho-nuclears, and occasionally more compact aggregations of cells. There is local loss of muscle nuclei. The adventitia is represented by dense connective tissue, amongst which are numerous capillaries with very swollen endothelium.

This investigation was incited by the discovery of severe intimal thickening in the main branches of the coronary arteries, considerably reducing their lumen, in a child with severe rheumatic carditis, who during life suffered from typical anginal pain. In order to see whether these changes were exceptional or usual in this disease, blocks, which included the main coronary arteries, were taken from the next eight fatal cases of rheumatic carditis that were submitted to autopsy. These were so taken as to include sections of the right and left coronary arteries near their origin, the right and left circumflex, and the left

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anterior and right posterior descending branches. Thus, in all, nine hearts have been examined, all from patients dying in an acute attack, or relapse, of rheumatic carditis, and all under twenty years of age, the average age being 14. All of these hearts showed changes in one or more of the main branches of the coronary arteries, which, though less intense than those in the first case, are essentially similar in nature. These changes affect the intima, the media, and the adventitia.

Intima. The intima shows patchy areas of thickening with a loose connective tissue. In most cases this tissue contains very few cells, but in some it is comparatively cellular, the cells being mainly lymphocytes, and they are most closely aggregated in the deeper parts of the intima at its junction with the media. The participation of elastic tissue in this intimal thickening varies enormously, not only from case to case, but in different places in the same case. In some the thickened patch is practically devoid of elastic tissue, and the internal elastic lamina is hardly disturbed. In others the internal elastic lamina is splayed out, and in others again it is scattered diffusely throughout the major part of the intimal tissue. So dense is it in some cases that it appears to have proliferated actively and not to owe its bulkiness to breaking up of the internal elastic lamina. In some sections it almost suggests that the thickening is due to a 'musculo-elastic' layer, such as occurs in the normal aorta. In one case (Case II) where this intimal thickening is fairly cellular, the cells are arranged in the form of a nodule with endothelial cells in the centre and lymphocytes at the periphery. This is the only suggestion of nodule formation seen in the intima. Intimal proliferation was present, varying in type and degree, in all the cases examined.

Media. The media shows changes varying in intensity from a loss of nuclei in the muscle-fibres to fairly dense cellular infiltration, with breaking up of the muscle-cells. In addition to these changes there is a vacuolation of the media very similar in appearance to 'l'état reticulaire' described by Rabé. The lesions, like those in the intima, are quite patchy and may be limited to a small portion of the circumference of the vessel. In some places the intimal reaction has apparently transgressed into the media, disorganizing it still further. Most of the patches of cellular infiltration and breaking up of the muscle are situated in the inner half of the media, in the position nearest to the intima, and this change is present in all the cases examined but one (Case IX). Two cases (I and IV), in addition to these changes described, show in the media small collections of lymphocytes lying in a hyaline matrix between and separating the muscle-fibres. These lesions present an appearance very suggestive of the medial lesion in the aorta, described by Giraldi (8) and others, on a miniature scale.

Adventitia. This layer in most of the cases showed an increase in its fibrous tissue and lymphocytic infiltration of varying intensity.

Fat stains showed no evidence of a fatty degeneration in the sections examined. It is possible that they may occur.

In these descriptions no attention has been paid to the perivascular sub-miliary nodule occurring in relation to the capillaries, nor to the lesions of the smaller branches of the coronary arteries and arterioles, as they have been fully dealt with by other workers. The main object of this paper is to show that the whole coronary tree is liable to damage in a rheumatic infection, and that the incidence of this infection is not confined to its smaller branches. From these observations it is hardly permissible to claim any specific nature for these changes. It is possible that they may occur in many infections, though we have not been able to find any record of such an occurrence. Similarly, the lesion may not be confined to the coronary arteries, but may be distributed throughout the vascular tree, as is suggested in Pappenheimer and von Glahn's findings; but in the one case (Case II) in the series in which other arteries were examined these proved to be normal. The lesions described appear to correspond very closely to those described by Rabé and by Pappenheimer and von Glahn, but the essential nature of the lesion is difficult to decide. The intimal lesions on the whole show very little evidence of an inflammatory type of reaction, yet in one or two cases the intimal proliferation is cellular, and this, with the nodule-like formation in Case II, suggests that the whole reaction is inflammatory, upon which degenerative changes quickly supervene. The medial lesions are more definitely inflammatory in type, and it would appear that we are here dealing with a general 'panarteritis'. If this is so, it obviously opens up large questions on the aetiology of arterial disease generally, but until these observations have been amplified and controlled by further work, speculation is perhaps better avoided. Clinically it is interesting to note that the one patient exhibiting definite anginal pain should prove to have coronary lesions much more severe than is usual in this disease, although Gallavardin (7), describing a case with similar pain, states that the coronaries were normal, but, judging from his paper, the examination made was not very exhaustive.

My thanks are due to the physicians and pathologists of the Bristol General Hospital and Bristol Royal Infirmary, by whose kindness I was enabled to examine the material which forms the basis of this paper. The work has been done under the tenure of a Colston Research Fellowship.

Conclusions.

1. The main coronary arteries are usually affected in rheumatic carditis.
2. The lesion is a general panarteritis composed of:
    (a) Intimal thickening more or less cellular.
    (b) Degenerative and inflammatory lesions of the media.
    (c) Inflammatory infiltration and fibrosis of the adventitia.

APPENDIX.

Abstracts of Cases.

Case I. Male, aged 14. Fatal relapse of carditis, the last of many. P.M. Complete symphysis pericardii. Heart much enlarged. Mitral and tricuspid stenosis; recent rheumatic vegetations in mitral and aortic valves.

This case was remarkable clinically for the severe attacks of typical anginal pain which the boy experienced.

Case II. Female, aged 14. She died in an acute exacerbation of a long smouldering rheumatic carditis. P.M. Heart much enlarged with recent pericarditis and acute rheumatic endocarditis of aortic and mitral valves and left auricular wall.

Case III. Female, aged 14. She died in a first severe attack of chorea insaniens. P.M. Heart dilated. Recent rheumatic mitral endocarditis.

Case IV. Male, aged 14. He died in an acute attack of rheumatic carditis. P.M. Recent intense pericarditis and mediastinitis. Heart enlarged. Recent rheumatic vegetations on mitral, tricuspid, and aortic valves. Free fluid in pleurae and peritoneum.

Case V. Male, aged 5. He died in an acute relapse of a long smouldering rheumatic carditis. P.M. Adherent pericardium. Heart enlarged—some shortening of the chordae tendineae of the mitral valve. Recent rheumatic mitral and aortic endocarditis.

Case VI. Female, aged 7. She died in an acute exacerbation of rheumatic carditis. P.M. Adherent pericardium. Heart much enlarged. Chronic and acute rheumatic, mitral, and aortic endocarditis. Acute rheumatic endocarditis of left auricular wall.

Case VII. Male, aged 13. He died in a first acute attack of rheumatic carditis. P.M. Recent pericarditis. Heart enlarged. Mitral and aortic rheumatic endocarditis.

Case VIII. Male, aged 19. He died in an acute relapse of rheumatic carditis. P.M. Basal pericarditis. Heart much enlarged. Shortening of chordae tendineae of mitral valve. Recent rheumatic endocarditis of all four valves.

Case IX. Male, aged 19. Previous attack of rheumatic carditis, dying of pneumonia. P.M. Heart enlarged. Mitral stenosis with recent rheumatic vegetations along the free edge.

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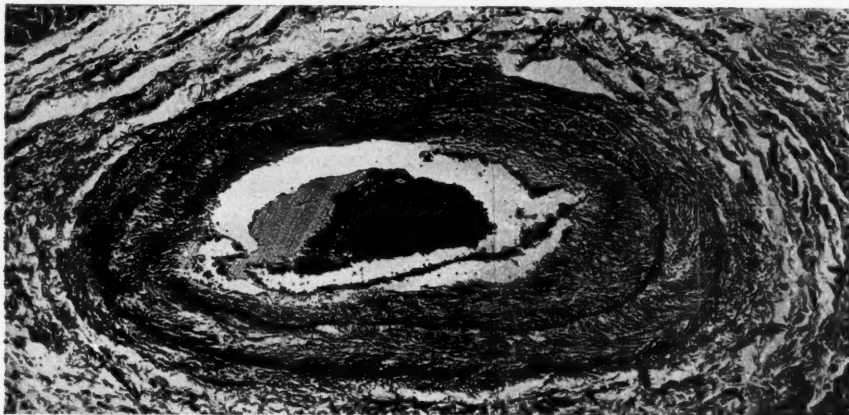
FIG. 1. Case 1. A section of the right coronary artery showing the intimal proliferation with very little disturbance of the internal elastic lamina, and the adventitial fibrosis. Orcein and van Gieson. × 75.
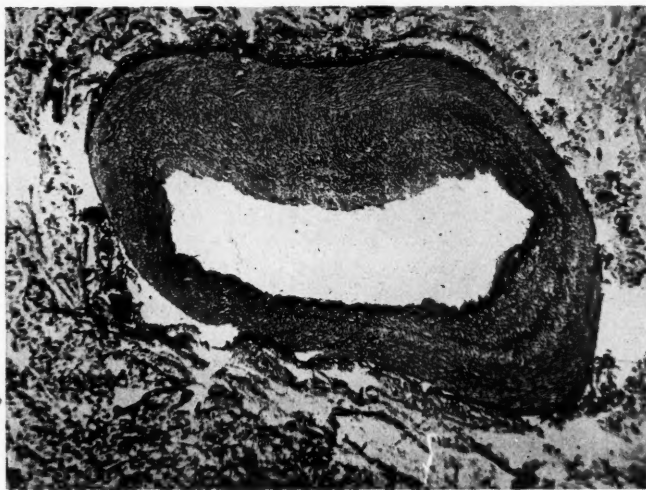
FIG. 2. Case 1. A section of one of the descending branches of the left coronary artery showing marked intimal thickening with splitting up and splaying out of the internal elastic lamina. Orcein and van Gieson. × 25.
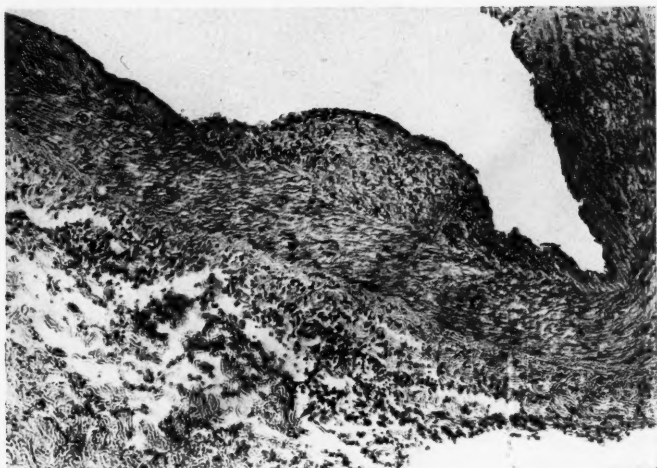
FIG. 3. Case 2. A section of the right coronary artery showing nodular intimal thickening. There is a nodule-like formation in the centre of which are endothelial cells. The section also shows the cellular infiltration of the adventitia. Haematoxylin and eosin. × 120.

FIG. 4. Case 2. A higher power view of the preceding section showing the endothelial cells in the centre of the 'nodule'. Haematoxylin and eosin. × 300.

FIG. 5. Case 1. A section of one of the descending branches of the right coronary artery showing *l'état réticulaire* of the media.   Haematoxylin and eosin.   × 300.
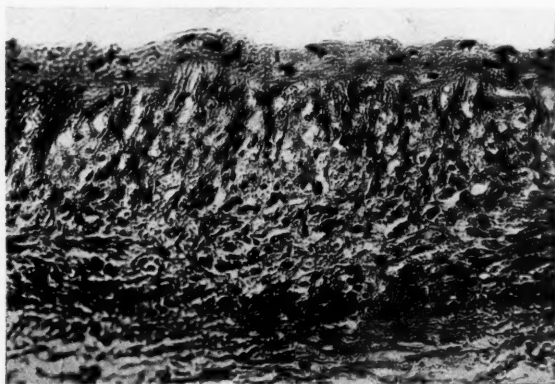
FIG. 6. Case 2.   A section of the circumflex branch of the right coronary artery showing the disorganization and cellular infiltration of the media.   Iron Haematoxylin and van Gieson.   × 300.
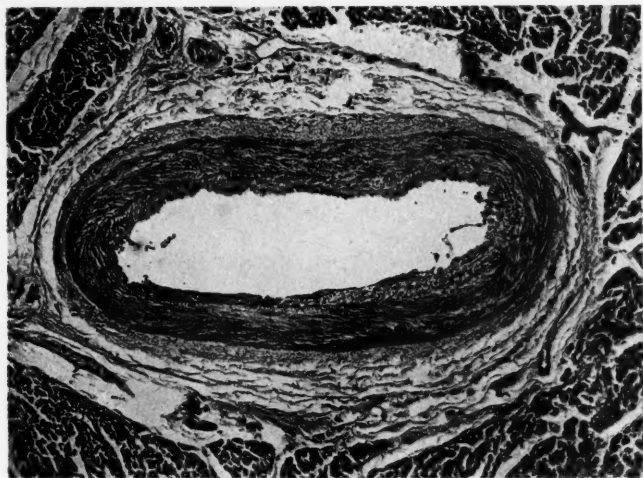
FIG. 7. Case 1.   A section of one of the descending branches of the left coronary artery showing a compact cellular focus between the muscle-fibres, also some intimal thickening and adventitial fibrosis.   Haematoxylin and eosin. × 100.
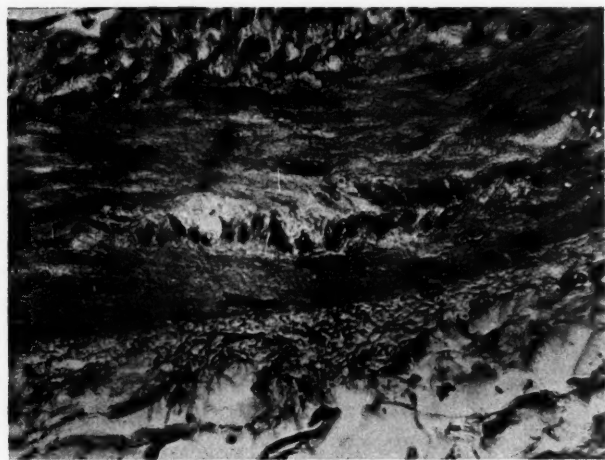
FIG. 8. Case 1.   A higher power view of the medial lesion in the preceding figure.   × 300.

ENDEMIC BACILLARY DYSENTERY IN ABERDEEN [1]

By A. M. FRASER and J. SMITH

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DURING the World War exceptional opportunities occurred for the study of bacillary dysentery from the clinical, pathological, and bacteriological aspects. Investigations into dysentery caused by the Shiga and Flexner types were reported by various English workers—Rajchman and Western (32), Fildes (12). Glynn (18), Murray (28), Fletcher (14), Gettings (17), and Dudgeon (11). In 1919 Andrewes and Inman (2) correlated the various types of the Flexner dysentery bacilli and produced a serviceable serological classification of these organisms. During this period certain Continental workers were also investigating this disease. Thus Kruse (24), who had previously classified the dysentery bacilli into eight groups, A, B, C, D, E, F, G, H (not including the Shiga type), added two further types, I and J. Schmitz (35) described a bacillus obtained from dysentery cases which resembled Shiga's organism in its cultural properties, except that it formed indol.

In recent years outbreaks of dysentery and enteritis have been found, on occasion, to be due to late lactose-fermenting organisms allied to the Flexner dysentery group. Sonne (38) found that the main cause of dysentery in Copenhagen was a late lactose-fermenting bacillus. D'Hérelle (19), in France, and Øhnell (30), in Sweden, also found these organisms to be associated with causes of dysentery. Andrewes (1) suggested the name *B. dispar* for lactose-fermenting members of the dysentery group, which he obtained from cases of suspected dysentery and from convalescents. Thjøtta (39), in Norway, while investigating cases of dysentery, obtained forty strains of Flexner dysentery bacilli (Thjøtta group II) and twenty-five strains of the Sonne type (Thjøtta group III). He explained that the less frequent finding of the Sonne type was due to the fact that this organism often caused a mild diarrhoea that was not sufficiently serious to necessitate the services of a physician, with the result that the cases were not subjected to bacteriological investigation.

In Japan, from children who clinically were suffering from dysentery, Mita (27) isolated bacilli similar in their cultural characteristics to the type described by Sonne. These strains he called para-dysentery bacilli. In a later paper Thjøtta and Sundt (40) showed that the Sonne bacillus produced both an endotoxin and an exotoxin. The endotoxin was more marked in effect, and produced intestinal symptoms in rabbits and mice. The exotoxin was milder in

its action as compared with the exotoxin of *B. dysenteriae*, Shiga, and produced paresis in rabbits, while mice reacted non-specifically to it. In Australia, Patterson and Williams (31) recovered the Sonne bacillus from patients suffering from enterocolitis, dysentery, and summer diarrhoea.

A further attempt at classification was made in 1927 by Kalic (21), who attempted to correlate the findings of Andrewes (2), Kruse (24) and Aoki (3).

TABLE I.

Classification.

Andrewes.	Kruse.	Aoki.
V	B or C	No corresponding type
W	No corresponding type	„ „ II „
X	„ „ „	II
Y	„ D „	I
Z	H	X
Shiga	Shiga	VIII (Shiga)

He also found that Aoki's types III and V were identical, that the Kruse E type corresponded to the Sonne III type, and that Aoki's types VII and XI were not dysentery bacilli.

In Britain dysentery became a notifiable disease in August 1919, and since that time statistics are available as to its occurrence. The notified cases for England and Wales and for Scotland are given in Table II.

TABLE II.

England and Wales.

Year.	Cases notified.	Deaths registered.			
		Total.	Bacillary.	Amoebic.	Unspecified.
1919	1638	435	—	—	—
1920	1169	254	—	—	—
1921	1193	261	17	11	233
1922	757	216	21	10	185
1923	458	149	12	13	124
1924	356	130	13	8	109
1925	293	135	13	11	111
1926	486	142	11	14	111
1927	440	95	—	—	—

Scotland.

Year.	Cases notified.	Deaths registered.
1919	217	32
1920	276	18
1921	108	22
1922	42	8
1923	60	5
1924	42	9
1925	52	7
1926	256	14
1927	187	12

In the more complete records available for England and Wales, a striking feature is the proportion of unclassified cases in which dysentery has been given as the cause of death. Only a very small number of deaths are attributed to

bacillary dysentery, and it is not known what proportion of these, or, indeed of the total notified cases, have been bacteriologically proved.   In Scotland, notified dysentery appears without differentiation as to type, and shows from 1922 to 1925 an almost negligible incidence with a recrudescence in 1926 and 1927.

Apart from the statistical accounts, there is in the medical literature of the period an increase in the contributions dealing with acute intestinal infections. In these it is evident that the classical dysenteric features are not so frequent as formerly, and there is an increasing body of medical opinion which assigns the diarrhoeas to specific dysenteric infections, and points to the endemic character of the disease.   The literature presents descriptions of epidemics, usually of small proportions, caused by the Flexner and Sonne types.   Outbreaks due to Flexner types have been described by Dawson (10), Fitz-Gerald (13), Wade (41), Kinloch (23), Charles (7), Joseph and Manson (20), and Severn and Evans (36). A severe infection with central nervous symptoms is described by Breakey and Clayton (5), while Flexner dysentery as a cause of sudden death, with symptoms similar to food poisoning, has been recorded by Warren (42).   The epidemic described by Wade and Kinloch is of special interest on account of the large number of cases involved.   The milk-borne epidemic described by Kinloch, which occurred in Aberdeen in March 1919, involved 978 individuals and caused 72 deaths.   The epidemic described by Wade occurred in May 1921 in Ogmore Vale, in Wales, involved about 1,100 cases, and caused only 12 deaths.   Finally, Charles and Warren (8), in an important paper, show that cases of Flexner dysentery have been an everyday occurrence in the Newcastle area during the past year.

The association of dysenteric features with a late lactose-fermenting organism was noted in a small outbreak by Bamforth (4), and Nabarro (29) recovered a similar organism from cases of summer diarrhoea, and which he named *B. coli anaerogenes*.   In 1924, Smith (37) recognized the Sonne bacillus as the infective agent in an outbreak in Aberdeen, and since then it has been frequently found as a pathogen and recorded from various parts of the country. Contributions on Sonne dysentery from the bacteriological, clinical, and epidemiological sides have appeared from Fraser, Kinloch, and Smith (15), Channon (6), Clayton (9), Wiseman (43 and 44), Kerrin (22), Fyfe (16), Richards (33), and Charles and Warren (8).   Fyfe described a milk-borne outbreak, the first recorded in connexion with Sonne dysentery.

The trend of modern medical thought in relation to dysenteric infections is shown in an instructive contribution by Manson-Bahr (26), who emphasizes the factors in the spread of the disease and their importance to the public health—a striking contrast to the dearth of information contained in even authoritative manuals of hygiene of the present time.   The increasing acknowledgement of the organismal basis of diarrhoeic conditions is very satisfactory, and is, indeed, fundamental to their prevention and control.

I. *Statistical Analysis of Cases in Aberdeen.*

For the purpose of statistical analysis cases of bacillary dysentery occurring in Aberdeen since August 1919 have been classified into three groups.   The first group consisted of those cases due the Flexner type of bacillus, the second of cases due to the Sonne bacillus, and the third of cases—clinical dysentery—in which no bacteriological evidence was obtained.   No cases of dysentery due to the Shiga bacillus have ever been encountered in this area, and further, all cases of dysentery contracted abroad and notified after arrival in this country have been excluded.   The annual distribution of the cases of dysentery is given in Table III.

TABLE III.

Annual Distribution.

Year.	Flexner Dysentery.	Sonne Dysentery.	Clinical Dysentery.
1919	1	—	0
1920	4	—	6
1921	21	—	0
1922	0	—	5
1923	0	4	0
1924	0	0	0
1925	5	8	0
1926	12	47	1
1927	9	41	6
1928	95	47	10
Totals	147	147	28

It is evident, therefore, that Flexner dysentery was almost epidemic during the year 1928, and the majority of the cases occurred during the late summer and autumn, whereas Sonne dysentery has shown practically the same prevalence during the years 1926, 1927, and 1928.

Age incidence.   All told, 322 cases of dysentery were reported as having occurred during the period 1919–28, and their distribution over the various age groups is given in Table IV.

TABLE IV.

Distribution in Age Groups.

Age Group.	No. of Flexner Cases.	No. of Sonne Cases.	No. of Clinical Cases.	Total Cases.	Percentage in Age Groups.
0–5	59	108	7	174	54
5–15	37	16	6	59	18·3
15–25	6	5	3	14	4·3
25–45	22	7	7	36	11·1
45–65	15	6	4	25	8·0
65 and over	8	5	1	14	4·3

Cases due to Flexner dysentery occurred mainly among individuals under 15 years of age.   Thus in the age-period of 0–5 years there were 59 cases, while in the age-group 5–15 years there were 37 cases.   The majority of the Sonne dysentery cases occurred in the age group 0–5 years, since out of a total of 147

cases no fewer than 108 occurred at this age-period.   As will be seen later, the example of individuals cannot be regarded as a random one on account of the special incidence of the disease among hospital cases.   The number of clinical cases of dysentery (unclassified bacteriologically) occurring in the various age-groups was very small, so that no definite conclusion could be drawn from them. It is evident that bacillary dysentery, as seen in Aberdeen, is essentially a disease of childhood, and more especially confined to children under 5 years of age.   A definite increase in the number of cases has occurred in the age-groups 25–45 and 46–65.   The explanation of this phenomenon probably lies in the fact that the males and females of these groups are more frequently closely associated in family life with young children.

Incidence of dysentery in first 5 years of life.   The cases of dysentery occurring in the first 5 years of life have been distributed over smaller age-periods in Table V.   In both the Flexner and the Sonne types of the disease

TABLE V.

Distribution of Cases in First 5 Years of Life.

	0–½ yr.	½–1 yr.	1–2 yrs.	2–3 yrs.	3–4 yrs.	4–5 yrs.
Flexner	9	9	14	11	8	8
Sonne	13	21	30	23	11	10
Clinical	0	1	3	3	0	0
Totals	22	31	47	37	19	18

most cases have occurred at the 1–2 year age-period, but on the other hand there was no evidence of protection during the early months of life, since 22 cases occurred at the age-period 0–½ year.

Mortality incidence in age-groups.   The number of cases dying from dysentery has been small, since 12 deaths out of 147 cases of Flexner dysentery, 7 deaths out of 147 cases of Sonne dysentery, and 1 death out of 28 in the clinical group unclassified bacteriologically have occurred.   The findings show a percentage death-rate of 8·1 for Flexner dysentery, 4·08 for Sonne dysentery, and 6·2 for all types of cases.   The deaths from Flexner dysentery were widely distributed over the various age-groups, whereas the deaths from Sonne dysentery have all occurred in the first 5 years of life.   Twenty-four cases of Flexner dysentery occurred in individuals of 45 years and over, and of these 6 or 25 per cent. died.   The fatal cases were inmates of a mental hospital, and asylum dysentery has always been regarded as a disease of serious import.

Relationship to sex.   When the relationship of dysentery to the sexes was examined, it was seen that out of a total number of 322 cases 140 were males and 182 were females.   The male to female ratios showed no marked difference in the age-groups 0–5 and 5–15, but in the remaining age-groups the females showed a distinct preponderance.   This is what would be expected if dysentery is regarded as a disease of childhood, when the adult female section of the population have more intimate opportunities for infection than the males.

Seasonal incidence of dysentery cases. The cases are distributed according to the months of the year in which they occurred in Table VI.

TABLE VI.

Seasonal Incidence.

	Flexner Dysentery.	Sonne Dysentery.	Clinical Dysentery.	Total.
January	11	14	3	28
February	8	3	3	14
March	1	27	—	28
April	2	8	2	12
May	5	11	2	18
June	10	8	—	18
July	8	7	3	18
August	13	10	1	24
September	32	18	—	50
October	21	15	5	41
November	21	8	5	34
December	15	18	4	37
Totals	147	147	28	322

During the past year when Flexner dysentery assumed almost epidemic proportions, the majority of the cases occurred from August to December. In 1921 the Flexner cases also occurred in the late summer and autumn months of the year. The Sonne cases have not shown any marked seasonal distribution.

In previous years when enteritis of infants was prevalent, the disease had a seasonal distribution occurring mainly in the late summer and autumn months of the year. There seems to be little doubt but that infantile diarrhoea in the past was due to some unrecognized type of dysentery bacillus.

Relationship of cases to environmental condition. The cases of dysentery have been allocated to the size of house in which they occurred in Table VII.

TABLE VII.

Number of Cases in Houses containing

	1 room.	2 rooms.	3 rooms.	4 rooms.	5 rooms and over.	Number in institutions.
Flexner	24	37	20	3	3	60
Sonne	9	13	7	5	18	95
Clinical	3	10	7	6	1	1
Totals	36	60	34	14	22	156

The majority of cases occurring outside institutions have taken place in the smaller types of houses, but this was only what was to be expected since the bulk of the population was housed in the smaller types of dwellings. A noteworthy feature was the occurrence of quite a large number of cases in institutions, and there is no doubt that the control of the infections due to dysentery bacilli in children's wards and in asylums is an extremely difficult matter. Further, the relative incidence of cases occurring in the homes and in the institutions was emphasized by the fact that in these latter establishments the children were under constant medical care. Consequently, when a case of diarrhoea did

occur, there was every chance of obtaining entire bacteriological proof. The number of cases which occurred in institutions suggested at once that hundreds of unrecognized cases must have been constantly occurring among the population generally.

Familial incidence of cases. The familial incidence of the disease was next examined. Flexner dysentery occurred in 60 families. In 44 families single cases occurred, in 9 families 2 cases, in 4 families 3 cases, in 2 families 4 cases, and in 1 family 5 cases. The familial incidence (44) of Sonne dysentery was distributed as follows: in 39 families single cases occurred, in 4 families 2 cases, and in 1 family 5 cases. Dysentery, unclassified bacteriologically, was distributed thus: in 20 families 1 case, in 1 family 2 cases, and in 1 family 5 cases. From this it will be seen that dysentery, apart from institutional practice, has a relatively low infectivity. This institutional incidence, especially in the case of Sonne dysentery, would be a disturbing reflection on institutional control were it not borne in mind that many are of a type so mild as to probably escape notice except in such institutions as provide adequate bacteriological facilities for prompt diagnosis.

II. *Clinical Description and Treatment of Bacillary Dysentery as occurring in Hospital Practice.*

It is proposed now to give an analysis of the symptomatology of Flexner and Sonne dysentery as seen in hospital practice during the years 1926, 1927, and 1928. This description is based on fifty-seven cases of Flexner and fifty-nine of Sonne dysentery. Clinically the two types of infection cannot be distinguished.

The onset of the disease was characteristically sudden, the clinical manifestations being maximal during the first twenty-four hours. In this survey it was found that in eighty-three of both Flexner and Sonne cases the onset was abrupt, the symptoms being general and alimentary, frequently the latter alone being present.

General manifestations. In 53 per cent. of cases the temperature was raised to a variable degree from 99° F. to 103° F., the majority being in the region of 99·4° F. The several registers of 102° F. and thereby were exceptional, and not at all characteristic of this series. In the remaining 46·5 per cent. the temperature was in the main normal, or occasionally subnormal. The subnormal type of temperature had no prognostic significance, and in no case was either a collapse temperature or hyperpyrexia noted.

In such as were pyrexial the temperature did not as a rule endure for more than forty-eight hours, and frequently subsided in twenty-four. The brevity of the fever might account for its non-observance in many cases which were not under continuous observation. Hospital cases showed definitely, especially in children, that the disease could be established without any pyrexial manifestation.

An increase in the pulse-rate was manifest in 71·4 per cent. of cases. In the main the increase was proportionate to the pyrexia, but in the apyrexial cases an increase of from ten to twenty beats per minute was evident. Apart from the moderate tachycardia no cardiovascular symptoms of any significance were present. In 28·6 per cent. there was no increase in the pulse-rate, and these did not differ in severity from the others.

Alimentary symptoms. Nausea as intimated by adults and older children presented in 17·6 per cent. of cases, and was such as is found in moderate toxaemias. Vomiting was present in 30·5 per cent. of Flexner and 94 per cent. of Sonne, but was not of an urgent variety, and in no case did it cause alarm. Nausea, vomiting, and the other alimentary features appeared simultaneously.

The sign characteristic above all others of bacillary dysentery is the exhibition of loose stools containing in many cases blood and mucus. In 91 per cent. of cases the stools were loose and of varying frequency. They numbered from one to fourteen per diem, and consisted of from small semi-formed masses to the profuse watery variety. Mucus was present in a similar number, as flakes or giving a general glairy appearance to the more formed stools. The general appearance of the stool in infants was less definite, and more generally was greenish in colour.

The presence of blood in the stools was noted in 57 or 60 per cent. of the Flexner cases, and in only 13·5 per cent. of Sonne cases. This imparted, in adults especially, a darkish colour to the stools, but in many cases it occurred, especially in children, as bright red streaks on the outer surface of the stools. Generally the odour of the adult stool was more foetid than usual, while that of infants was but little changed. In fact, in infants, apart from the appearance of blood in the stool, there is but little to distinguish the proved dysenteric stool from that of the so-called simple diarrhoea.

Tenesmus was not a prominent feature, and was at no time distressing, and the bowel manifestations did not, as a rule, endure for more than two days, and were commonly followed by constipation.

Abdominal examination revealed variable signs. On inspection no abnormal features were noted in 75 per cent. of cases, while in the remaining 25 per cent. a moderate generalized distension presented. This feature was seldom distressing. Abdominal pain was complained of in 32·1 per cent., and this was mainly along the track of the colon and only occasionally generalized. Tenderness on palpation was elicited in 15 or 26·7 per cent. of cases. Occasionally tenderness was generalized, but the particular localization was along the course of the colon and was usually more evident at the sigmoid, where, in a very few cases, an increased tonic condition was demonstrable.

Respiratory symptoms. In Flexner dysentery respiratory symptoms occurred in 14 or 25 per cent. of cases. Bronchial catarrh of an almost uniformly mild type appeared at a variable period in relation to the other symptoms. Most frequently it followed immediately after the onset, but in no case in this series was it of serious import.

In cases of Sonne dysentery the respiratory system was frequently involved in a catarrhal process.   This either preceded the onset of the acute symptoms or was coincident with them and was of varying degree.   Nasal catarrh was present in 27·1 per cent. of this series, and bronchial catarrh râles, cough, and increased respiratory rate in 39 per cent. of cases.   A definite broncho-pneumonia supervened with fatal consequences in two cases, but apart from these cases respiratory catarrh was not serious.

Symptoms referable to central nervous system.   Atypically, in certain Flexner cases, the toxaemia was so rapidly established as to produce central nervous manifestations before any of the usual dysenteric symptoms were present.   Four such cases were observed, and were sent to hospital notified as meningitis.   In three there was a history of convulsions and persistent vomiting, accompanied in one case by delirium.   Examination failed to reveal any definite central nervous lesion.   More serious manifestations were noted in one case which was admitted as a case of meningitis.   In this instance there was a history of twenty-four hours' illness, commencing with irritability and progressing through delirium to a semi-conscious state in which he was admitted.   The pupils were contracted and reflexes modified in the following particulars : Kernig's sign was positive, and the plantar reflex was extensor on the right side, and the abdominal reflexes were absent.   Later the pupils became dilated and did not react to light, neck rigidity was present, and Kernig's sign became positive on both sides.   Examination revealed no abnormality in the cerebro-spinal fluid.   It was not until two days following admission that the typical dysenteric features became evident, and with their establishment came amelioration of the nervous symptoms and eventually recovery.

Sequelae.   In Flexner dysentery the notable feature of the cases described was the practically uncomplicated course of the disease apart from mild respiratory involvement, and the nervous features already mentioned.   Arthritis, ophthalmic, peritoneal, skin, and cardiovascular complications as seen at other times were entirely absent.

In Sonne dysentery complications, apart from the respiratory ones mentioned, were practically unknown in the hospital series, and except for an occasional loose stool, the condition cleared up well.   Constipation commonly followed the more acute stage.

Of the deaths seen in hospital, only one can be ascribed to dysentery alone. The others occurred in cases already suffering from additional acute infections such as whooping-cough, measles, broncho-pneumonia, and osteomyelitis.   The child dying of dysentery survived for only three days after the onset.   Enteritis was the first feature followed by profound toxaemia, dehydration, collapse, and death.

Second attacks were recorded in three cases of Flexner dysentery.   Of these, an adult male and female both had dysentery in 1919, and developed the disease again in 1921 and 1922 respectively.   The third case also, an adult female, had Flexner dysentery in 1919, and died of a second attack in 1920.

Differential diagnosis. The detailed analysis of the clinical symptoms of the hospital cases showed that 83 per cent. of both types of cases had an abrupt onset; vomiting was present in 30 per cent. of Flexner cases and 44 per cent. of Sonne cases; abdominal pain in 30 per cent. of both types; blood and mucus were present in the faeces in 60 per cent. of Flexner cases and in only 13 per cent. of Sonne cases. Many cases of both Flexner and Sonne dysentery became convalescent within twenty-four hours of the onset of the illness, and had re-covered completely within two days. From the clinical standpoint it would thus appear to be frequently impossible to distinguish mild cases of Flexner and Sonne dysentery from mild infections due to members of the Salmonella group. In fact, the exact diagnosis in many cases is only possible when the causative organisms are obtained by bacteriological methods from the faeces.

Treatment of bacillary dysentery. Apart from specific measures available, the treatment of Sonne and Flexner dysentery did not differ in any particular. So far the only serum available for Flexner dysentery is of the polyvalent variety, and the mild type of the disease did not warrant the routine ad-ministration of serum. The thirty-five cases in which serum was administered in doses from 20–40 c.c. did not show any marked acceleration in improvement, and the type of the disease did not justify the massive dosage rightly favoured during the War in the more severe Shiga dysentery seen in the Eastern theatres.

The administration of two drachms of sodium sulphate for adults, and pro-portionate doses for children, four-hourly, in the first twenty-four to thirty-six hours cleared the bowel well, and was frequently the only treatment (together with nursing) that was necessary.

Diet did not require modification except during the first three or four days and during this time warm fluids were given freely—plain water, barley water, albumin water—then milk, and fat-free chicken- and mutton-broth with cereals. The return to full diet was possible at the very latest within a week.

III. *Bacteriological Investigation.*

For the routine diagnosis of bacillary dysentery, the specimens of faeces, obtained as early as possible after the onset of the illness, were plated on McConkey's medium. After an incubation period of twenty-four hours, colonies were selected and inoculated into tubes containing the liquid carbohydrate media lactose, glucose, mannite, and dulcite, on to an agar slope, and into a plain broth tube. If, after an incubation period of twenty-four hours, the organisms were Gram-negative, non-motile, and gave the correct sugar reactions, they were tested for agglutination with a polyvalent Flexner serum prepared by immunizing rabbits with the V, W, X, Y, and Z strains, and with a serum pre-pared from a smooth Sonne strain. The extent of the work involved in the routine diagnosis and control of dysentery in the City and in the Municipal

hospitals may be judged by the fact that in 1926 835, in 1927 742, and in 1928 1,655 specimens of faeces were submitted for bacteriological examination.

Typing of Flexner strains.   Through the good offices of Dr. W. M. Scott of the Ministry of Health Pathological Laboratory, London, a number of Flexner strains obtained during the past year from patients in the City of Aberdeen and in the north-east of Scotland have been typed.   The results obtained are given in Table VIII, and are compared with those obtained by Charles and Warren (8) in Newcastle.

<div align="center">

TABLE VIII.

Typing of Flexner Strains.

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City or county in which patient resided.	No. of strains of various types isolated.				
	V	W	X	Y	Z
Aberdeen	0	2	8	2	102
Banffshire	0	2	0	0	17
Inverness-shire	0	1	0	0	0
Kincardineshire	0	0	0	0	1
Totals	0	5	8	2	120
Newcastle (Charles and Warren)	0	51	8	1	49

It will thus be seen that the chief cause of the Flexner dysentery has been a bacillus of the Z type, and only sporadic cases infected with the W, X, and Y types occurred, while no case due to the V type has been encountered in this area.

Duration of infectivity.   In all cases of Flexner and Sonne dysentery admitted to hospital, a systematic bacteriological examination has been made of the faeces.   Thus, in order that a case might be discharged from hospital, three consecutive negative examinations were required.

From the bacteriological records of the various cases, information was available as to the duration of infectivity of these cases of Flexner and Sonne dysentery.

Flexner dysentery.   In 57 cases, the bacteriological records were complete enough to show that: (1) In 37 cases the dysentery bacilli had disappeared within a week of the onset of the illness.   (2) In 5 cases the organisms were present throughout the first week and disappeared from the faeces in the second week.   (3) In 12 cases the faeces remained positive for two weeks and became negative in the course of the third week.   (4) In the remaining 3 cases the faeces remained persistently positive for three weeks and became negative in the fourth week.

Sonne dysentery.   In 53 hospital cases in which adequate repeated examinations of the faeces were made, the following results were obtained: (1) Forty-one cases had become negative within one week of the onset of the illness.   (2) Four cases were positive throughout the first week after the onset, but became negative during the second week.   (3) Four cases were still positive in the second week and became negative in the third week.   (4) Three cases

were positive in the third week and negative in the fourth. (5) The faeces from one case gave continuously positive results for seven months.

For the most part the duration of infectivity was comparatively short, especially so was this the case with the Flexner infections, since the faeces from all the fifty-seven cases became negative within four weeks. In the Sonne infections only one case remained persistently positive for a considerable period.

IV. *The Spread and the Control of Dysentery.*

Ledingham and Arkwright (25) state that outbreaks of bacillary dysentery are rarely due to healthy carriers. Saquépée (34) declares that cases with the mild form of the disease are mainly the cause of the spread. Manson-Bahr (26) concludes 'that the true prophylaxis of bacillary dysentery rests upon general hygienic principles combined with the recognition and adequate isolation of subacute and chronic cases of the disease'.

In the spread of bacillary dysentery as seen in Aberdeen it is believed that the healthy carrier plays practically no part, the subacute case and the convalescent carrier are entirely responsible for the continual spread of the disease. The investigation on the duration of infectivity of these cases showed that it was only in an exceptional case that dysentery bacilli were found in the faeces one month after the onset of the illness. The disease, therefore, is spread from individual to individual by the scattering of infectious discharges.

From a consideration of the distribution of dysentery cases among the general population it will be apparent that the strict observation of ordinary personal hygienic measures should suffice to limit the spread of the disease. The only danger of widespread infection lies in the possibility of contamination of food supplies, for example, milk by an infective person. Here again careful personal hygiene would obviate any spread. From the administrative point of view there are already, in various acts, ample powers for dealing with such possibilities.

The institutional control of dysenteric infections has called for more strict attention. Repeated ward outbreaks which had their genesis in newly admitted cases demonstrated in many instances the fallibility of clinical observation as a means of diagnosis, and also reflected perhaps on the veracity, and certainly on the observation of parents, whose description of the child's previous history did not coincide with the bowel manifestations seen immediately after admission.

A preliminary period of observation of all admissions to the Ailing Babies Ward became necessary, and during that time clinical and bacteriological methods were applied to ascertain whether the child was infective and, if the faeces were negative, the child was then admitted to the general ward. The control of dysentery in general and in institutions requires the recognition of the simple diarrhoeas as being possibly of dysenteric origin. A more prolonged

preliminary observation was enforced in cases which had diarrhoeal symptoms, while their development after admission to the general ward was dealt with in the first instance by prompt isolation until their nature had been proved. Cases of proved dysentery were removed to a ward set aside for that disease.

Of the utmost importance in the control of dysentery in a children's ward is the organization of the nursing. Here it was found best to allocate the duties to two teams, one to conduct the preparation and administration of the feeds and the toilet of the head and neck, and the other to perform the remaining toilet and all other changing. Cleansing of linen in the ward is not allowed. Nurses are strictly forbidden to participate in any duties other than those allocated. The hours off duty are so arranged that there is always a sufficient number of each team on duty to carry out the work of the ward. In addition, no nurse is drafted to the ward until she has had some months' experience and training, and so is able to appreciate the importance of various measures, in relation to the spread of infection.

V. *Summary.*

From the figures submitted, it will be apparent that dysentery due to the Flexner and Sonne organisms is endemic in Aberdeen. A large proportion of the cases were sporadic, and inquiry failed to establish any connexion between the individual sporadic cases or to prove a common source.

The disease has been one of childhood, with increased infection among those in attendance on children. Of the Flexner cases 65 per cent. occurred in children of 15 years and under, and of the Sonne cases there was an increased incidence in the early years, since cases in the 0–5 years age group accounted for 68 per cent. of the total.

The seasonal incidence of Flexner dysentery, while confined to summer and autumn in the earlier years under survey, showed in the last two years a prevalence throughout the whole year, with a tendency to increase over the second half of the year. Sonne dysentery showed a uniformity of incidence throughout the whole year.

The mortality from Flexner dysentery was least in early childhood and increased with age, while in Sonne dysentery the total mortality occurred in the first five years of life.

A favourable feature of the prevailing type of the disease was the entire absence of the debilitating sequelae, so common in the classical type. It may be that this mildness is but one of the cyclical variations in the biological activity of the organism, and in time we may again experience a recurrence of the more severe variety.

In Aberdeen the causal agents of the disease have been found mainly to be *B. dysenteriae* Flexner Z, and *B. dysenteriae* Sonne. Sporadic cases due to the Flexner types, W, X, Y, have also been encountered.

An investigation into the duration of infectivity of cases of Flexner and

Sonne dysentery has shown that dysentery bacilli rapidly disappear from the faeces after the termination of the acute stage of the disease. An examination of the faeces from 57 cases of Flexner dysentery showed that all had become negative within a month of the onset, and in a similar examination of 53 cases of Sonne dysentery only one individual was found to harbour the causative organism a month after the onset.

The disease was mainly spread by direct contact with the infectious discharges of subacute cases and convalescent carriers.

Ordinary hygienic measures should suffice to limit the spread of the disease. For the control of institutional outbreaks the prophylactic measures adopted are discussed in detail.

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ON THE CLINICAL SIGNIFICANCE OF RIGHT BRANCH BUNDLE BLOCK [1]

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With Plate 15

THE prognostic value of any given sign in disease of the heart is always a difficult problem. An organic lesion confined to one branch of the auriculo-ventricular bundle is not one which should be regarded as jeopardizing life. A bundle branch block may be present for many years and the heart maintain a reasonable efficiency.

The important factor in prognosis is not the block itself but the pathological lesion causing the block. A bundle lesion should not be regarded as a definite pathological entity but rather as a significant feature in the total of myocardial damage.

In general, the prognosis in bundle branch block as such is considered as bad. Price (8), in his text-book on diseases of the heart, writes: 'When the condition is permanent the prognosis is usually very unfavourable.' Willius (13), who has carefully studied the condition, has written that the prognosis is bad. In 138 cases of patients having aberrant QRS complexes in all leads of their electrocardiograms the average duration of life from the time of examination was eight and one half months.

The prognosis in the eighty cases here studied seems to differ according as they belong to one or other of the following three groups of cases:

Group I, the cardiovascular degenerative group, consists of 50 patients first seen at the average age of 59 years. Ten of these—20 per cent.—have since died, at an average age of 59·3 years.

Fifteen are at present untraced, and 25 are alive, all of whom, if not at present regularly attending the hospital, have been recently seen. One man, aged 57, who has been under observation for the last fourteen years, is at work as a musician. One who has been under observation for nine years is, at the age of 66, doing manual work, and others who are at work have been under observation for seven or more years.

In Group II, the syphilitic group of seventeen cases in which there was clinical evidence of cardiovascular syphilis, the average age of first attendance of which was 45 years, nine are already dead, at the average age of 45, four are untraced, four are attending the hospital, two of whom are in the wards with signs of gross congestive failure.

[1] Received September 16, 1929.

In Group III, the rheumatic group, we have eleven cases of rheumatic carditis with mitral stenosis, of which one has died at the age of 38, two years after her first attendance. Seven are still attending and three are untraced.

These facts show, therefore, that the prognosis in these three groups is quite different.

In the second group, the syphilitic, the electrocardiogram suggesting right branch block is significant of grave cardiovascular disease. The prognosis is bad, the average age of death of the recorded cases being 45 years. The majority of patients do not live for more than two years after the first record has been obtained.

In the first group the prognosis is much better. The average age at which the patient first attends the clinic is much higher—60 years. The average age of death is 60 years. In our experience 20 per cent. of persons aged 60 as compared with over fifty per cent. of an average age of 45 years in Group II have died, and of the majority one has been under observation for 14 years, and others under our care for 7 and 9 years. In the third—the rheumatic group—one only has died.

As it is probable that the progress in branch bundle block is dependent entirely on the aetiology of the underlying condition it is desirable to consider the frequency of its occurrence in each group. In the first—the cardiovascular degenerative group—we have not been able to estimate the frequency of the condition in regard to the whole group of cardiovascular degenerative conditions, by an estimation in our clinic Dr. Downie has found recently that in twenty-five cases of complete auricular ventricular block twelve fall into this group.

In the syphilitic group we have seventeen cases all with aortic regurgitation, whereas the total number of cases of syphilitic aortic incompetence who have attended our clinic during the last fourteen years is about a hundred.

Of the thirty cases of syphilitic aortic incompetence attending the hospital this year which I have reviewed, four show evidence of right bundle block.

In conjunction with these figures and with the fact that the average age of first attendance of the patients in this group in our series is 45·5 years, certain points in the report edited by Wells (12) on 10,000 recruits examined at the Heart hospital are of interest. Of the 10,000 cases 307 had clinical signs of aortic incompetence. Of these only eleven gave a history of syphilis, seven of which cases gave a definite history of rheumatic fever. He considered that the investigation of these cases led to the conclusion that syphilis as diagnosed clinically is not of much importance as a cause of aortic incompetence between the ages of 18–41. Only 3·6 per cent. of the cases of aortic incompetence gave a history of syphilis, and of these 3·6 per cent.—two-thirds—gave a history of rheumatic fever.

In the age group 37–41 years, 1,413 recruits were examined; thirty-eight showed aortic regurgitation, 2·7 of the total number of cases of aortic regurgitation. Only ten of these cases, or 0·7 per cent. of the whole, gave no definite history of rheumatism. These figures suggest that syphilitic aortic incompetence is but seldom recognized clinically before the age of 40.

The average age of death for all the cases of syphilitic aortitis who died during the last ten years is 47·5; for those with branch bundle block in our series it is 45 years. On analysing the case records of twenty-two cases of right bundle block, published by Carter (1) in 1914, I have found that in his series three cases were those of luetic aortitis with positive blood Wassermann reaction. The physical signs were similar to those in our own records. In these three cases, one died at the age of 38, one at the age of 47, and the third case was described in the notes as 'very ill' at the age of 39. This seems to confirm the view of the seriousness of the prognosis of right branch block occurring in this aetiological group.

In the rheumatic group there are eleven cases, whereas Goodall (5) in an analysis of 1,000 cases of mitral stenosis occurring in his hospital and private practice found only two cases of right branch bundle block.

Pathology.

Eppinger and Rothberger (3) were the first to associate changes in the Q.R.S. complex with lesions of the two main branches of the auriculo-ventricular bundle. When the right branch was cut the normal ventricular complex was replaced by a diphasic complex of high amplitude.

In 1910 Eppinger and Stoerk (4) published the results of an electrocardio-graphic study dealing with bundle branch block. Two of their patients came to necropsy. In both cases lesions were demonstrated completely dividing the right branch. The electrocardiograms showed diphasic QRS complexes in all derivations of increased amplitude in derivations I and III and having a basic width exceeding the normal. The QRS complex was directed upwards in lead I and downwards in leads II and III.

In 1913 Rothberger and Winterberg (10) investigated the subject, but their curves did not agree with those of Eppinger in that the QRS complex in leads I and III had the same and not the opposite direction.

Lewis in 1916 conducted a series of experiments on dogs. Smith (11) in 1918 tied the descending branch of the left coronary artery in dogs, afterwards keeping the animals alive and studying their electrocardiographic curves. Recently Cowan and Bramwell (2) in this country and Willius and Keith (14)—Rothschild and Oppenheimer (19)—in America have made valuable contributions. Fahr, from theoretical considerations, has stated that the usual diagnosis of right and left bundle lesions is probably wrong and believes that what has been interpreted as a right bundle branch block is in reality a left block.

From a study of the literature it would appear that in the majority of the clinical cases showing this condition there is no lesion found on microscopic examination suggestive of any complete structural alteration in the conducting system as distinct from the myocardium as a whole.

In the study of our cases we have not found much definite evidence of progressive change, as illustrated in the electrocardiograms taken at monthly

intervals over a period of years. Although the majority of our cases were classified as right bundle branch conditions after the first tracing had been taken, we have found, in particular in the cardiovascular degenerative group, a certain number of cases in which poor voltage curves, showing at first left-sided preponderance and subsequently a slight lengthening or notching of the QRS complex and prolongation of the ventricular conduction time, have within the course of some years shown definite evidence of a right bundle branch block in the electrocardiogram.

There seems to be no evidence that records similar to these have been described in the clinic or in the literature. They appear to denote slowly progressive circulatory changes as have been previously described, resulting in increasing right ventricular ischaemia. They are of great importance in that they form another link between the clinical, the electrographic, and pathological picture.

In a paper in the *American Heart Journal* recently published Luten and Grove (7) write 'that the incidence of electrocardiograms showing left axis deviation and QRS of normal duration with inverted T_1 and upright T_3 is confined almost exclusively to patients who exhibit either coronary diseases or some other disease which makes the presence of coronary involvement more or less probable. Experimental and clinical data strongly indicate that these electrocardiograms represent impairment of conductivity in the right limb of the auriculo-ventricular bundle. Consideration of the arterial distribution of the limbs of the bundle makes it appear highly probable that the conduction defect is induced by the concomitant vascular defect.' The second of the special cases here described exemplifies this: a left side preponderance—no lengthening of the QRS; an inverted T_1 and a vertical T_3; later records show typical right branch bundle block.

Selected Case Reports.

Rheumatic group.

Case I. Ivy A., aged 24. Single.

Diagnosis: Rheumatic carditis. Failure. Mitral stenosis. Left branch bundle block.

As a child, 'growing pains', aged 8. ? Rheumatic fever.

In 1926, aged 22: Began to complain of attacks of pain, upper chest, left, radiating. Shortness of breath.

18.3.28. Progressively restricted exertion; symptoms progressively worse. Signs of failure. Admitted under Dr. Strickland Goodall, National Heart Hospital.

State: No pyrexia. Slight congestive failure, marked cyanosis. No peripheral oedema. Liver markedly enlarged. Spleen not palpable. Heart rate 90–100 per minute; regular. Heart markedly enlarged. Apex beat in 7th space left outside nipple line. Apical 'Canter Rhythm'. Apical systolic and diastolic bruits. Blood-pressure, 120–80.

Progress: From time to time attacks of 'biliousness', signs of gross congestive failure. Liver markedly enlarged. Peripheral oedema marked. Relieved by leeching, diuretin, digitalis therapy. Finally, general condition markedly improved, and on 2.6.28 the patient was discharged, to continue rest at home.

21.11.28. General condition improved; occasional slight attacks as when in hospital, but feeling much better. Gradually getting up. Electrocardiograph unchanged.

'Syphilitic Group'.

Case II. Alfred R., aged 47. Attended Dr. Goodall's out-patients'. On 14.5.28 he complained of substernal pain, especially in early morning, and on exertion. On walking fast the pain radiated down left arm. Duration 1 year.

State. A large, well-built, plethoric man, heart enlarged. Apex beat just outside nipple line in the 6th space, not heaving. Apical sounds, 1st modified, 2nd distinct. Base: aortic and pulmonary 2nd modified. There was a thrill in the neck. Long systolic and diastolic bruit 'to and fro' over aortic area. Blood-pressure 160–50 mm. Hg. arm, 180–60 leg. Brachial vessels thickened.

Urine: Sp. gravity 10–10. No albumin, no sugar.

Blood Wassermann: Positive. X-ray. Heart increased to left, aorta wide. Not aneurysmal.

Electrocardiogram showed regular rhythm. Inversion T in lead I. Right bundle branch block.

Diagnosis: Syphilitic aortitis, large heart. Right bundle branch block.

Progress: with rest, Pot. iodide and digitalis, general condition improved.

4.6.28. Pain in chest—worse. Extension down left arm to fingers on slight exertion. Pulse-rate 116 regular.

17.6.28. Apparently 'quite well', at work.

18.6.28. In early morning woke up in bed with 'tight feeling' across chest. Coughed, no sputum. As he was due to attend out-patients' hurried by tram to hospital. On arrival he was 'very ill', cyanosed; signs of acute oedema of the lungs. Treated immediately with atropine, morphia, and venesection, but without effect. Patient died.

Necropsy: Oedematous lungs with much frothy fluid in trachea.

Cardiovascular system: Pericardium normal. Heart markedly enlarged. Weight 36 oz. Left ventricle hypertrophied markedly. Right ventricle not hypertrophied. Auricles, right not distended; left, slight distension. Heart-muscle firm, 'speckled'.

Aorta: Wide, marked evidence syphilitic aortitis involving intima of whole of ascending arch and first part descending aorta. Crypts and evidence recent inflammatory changes.

Aortic valves: Slight incompetence. Otherwise healthy.

Mitral valves: Healthy.

Coronary arteries: Lumen patent. Atheroma of right and left coronary.

Microscopic appearance: Diffuse fibrous tissue replacement of heart-muscle.

Cardiovascular Degeneration.

Case III. William M., aged 60. At work as contractor until six years previously when pain in the chest came on gradually at work. It was a tight feeling in the right upper sternal region, after exertion; if he stood still the pain disappeared. Frequency 2–3 week. Short of breath on exertion. Four years previously the pain increased in frequency and severity and he gave up work. Three months previously an attack with pain extending down right arm to fingers, brought on by least exertion.

Brought to hospital; having had ten attacks since 3 a.m.

State: Sthenic plethoric man—ill; heart enlarged. Apex beat ? in nipple line, feeble. Heart-sounds: apical; first sound modified, short systolic murmur. Second sound at aortic and pulmonary base modified. Blood-pressure 150–95. Rate 90 regular.

Emphysema: No signs of congestive failure. Fundal, vessels tortuous. Brachials thickened, tortuous. Wassermann negative. Urine normal.

Electrocardiogram: Right bundle branch block.

Diagnosis: Angina pectoris.

Progress: Several attacks, pain relieved in part by amyl nitrite with rest, digitalization, venesection; general improvement.

On 16.12 the patient at 1 a.m. suddenly fell back dead.

Necropsy: Heart enlarged, weight 21 oz. Externally definite ' bruised ' appearance of left ventricle, near apex. Aorta slightly enlarged, comparatively healthy, few atheromatous plaques. Aortic valves normal. Right coronary lumen almost obliterated. Calcareous throughout course. Left coronary orifice narrowed. Lumen practically obliterated. Local thick atheromatous portion immediately proximal to recent thrombus. Circumflex branch similar.

Left ventricle hypertrophied, apical portion recently infarcted, darkened, involving almost whole thickness of myocardium, with large ante-mortem endo-cardial blood clot. There was a pale area involving a large part of the ventricular wall, the interventricular septum and left papillary muscle suggesting an area of old infarction. Right ventricle and auricles, no gross abnormality. Liver, kidney, spleen congested. Lungs normal.

Anatomical diagnosis: Sclerosis with terminal thrombosis of left coronary artery. Microscopically diffuse fibrous replacement of ventricular heart-muscle.

Case IV.   Rebecca F.. aged 55, Group 3. Complaint: shortness of breath and retrosternal pain on exertion.

Electrocardiogram:

22.1.23.   (1) Regular rhythm left side preponderance.   Extra-systoles ventricular.   (Fig. 4 *a*).

20.7.23.   (2) Regular rhythm definite evidence notching, *QRS* complex, suggesting early right branch block.   (Fig. 4 *b*.)

14.4.24.   (3) Widening *QRS* complex.   (Fig. 4 *c*.)

18.1.26.   (4) (Fig. 4 *d*).

26.10.28.   (5) (Fig. 4 *e*).

17.12.28.   (6) Definite right branch block.   (Fig. 4 *f*.)

Case V.   Male, aged 53.   First attended 20.10.13.   Complaint: shortness breath one year.

Electrocardiographic records:

(1) 9.4.17.   Regular rhythm, flat vertical P and T all leads.   ? Inversion T i. Left side preponderance.   (Fig. 5 *a*).

(2) 24.4.19.   Regular rhythm, extra-systole ventricular.   Left side pre-ponderance.   T i. inverted T ii. iii. vertical, good voltage.   (Fig. 5 *b*).

(3) 20.5.24.   Irregular rhythm.   Auricular fibrillation.   (Clinically at this time on one occasion fell unconscious for three hours, later two further attacks and subsequent attacks giddiness.)   (Fig. 5 *c*).

(4) Early 3.25.   Definite widening, apical notching, *QRS* complex. (Fig. 5 *d*).

(5) Late 1925.   Early right branch block.   (Fig. 5 *e*).

(6) Early 1928.   Definite right branch block, auricular fibrillation, ventricu-lar extra-systoles.   (Fig. 5 *f*).

(7) Late 1928.   As before.   (Fig. 5 *g*).

Conclusions.

Eighty cases of branch bundle block have been investigated clinically and electrocardiographically. In an aetiological classification they fall into three groups : the cardiovascular degenerative, the syphilitic, and the rheumatic. The clinical picture and the prognosis are different and distinct in these three groups.

The first is the cardiovascular degenerative group in which the majority of the cases have been placed, the prognosis is reasonably good.

In the second, the syphilitic group, the prognosis is bad.

The third, the rheumatic group, is composed essentially of younger people, and the prognosis is good.

I should like to express my thanks to Dr. Strickland Goodall for his advice, interest, and permission to make use of his cases, to the other physicians on the staff of the National Heart Hospital, and to Mr. Stowe who has taken the electrocardiographic tracings.

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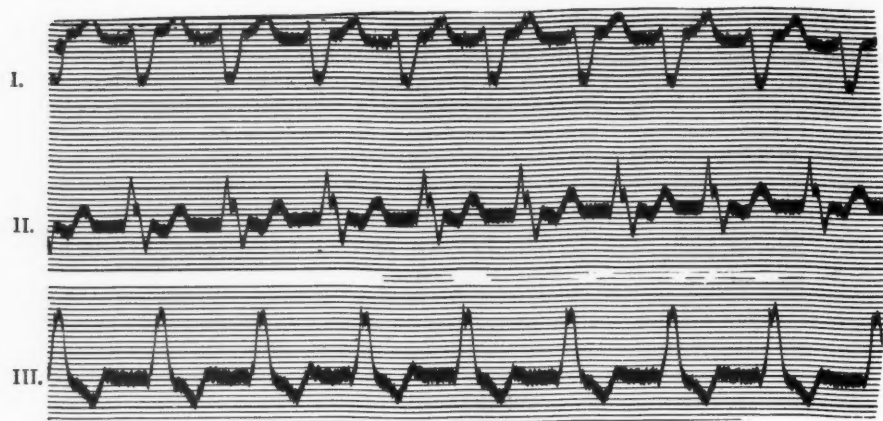
FIG. 1. Electrocardiogram of Case I.
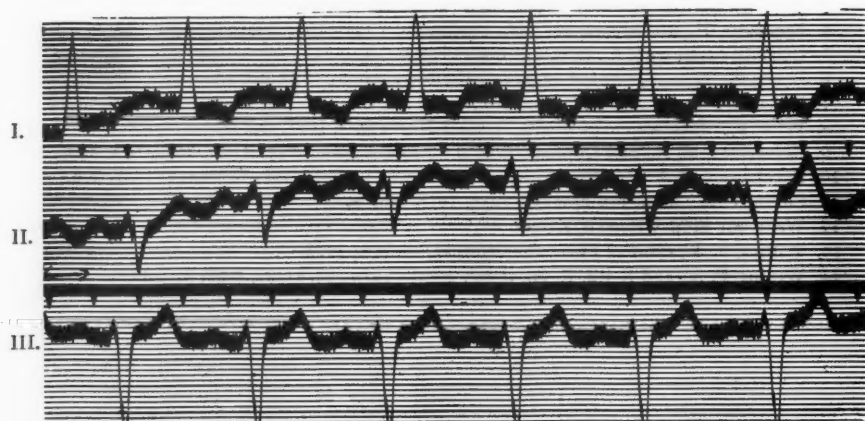
FIG. 2. Electrocardiogram of Case II. (Scale 0·2 sec.)

FIG. 3. Electrocardiogram of Case III. (Scale 0·2 sec.)
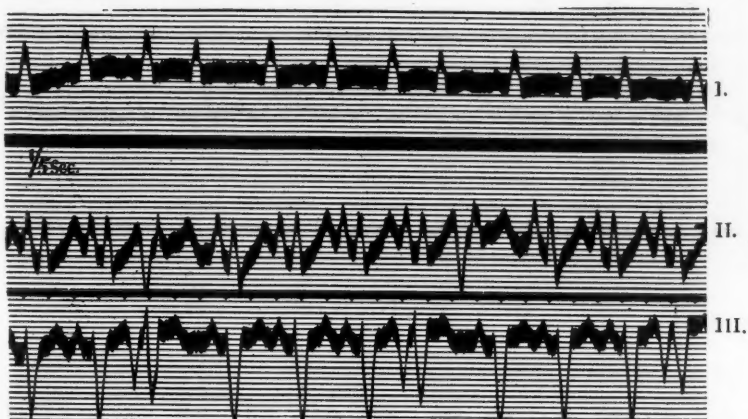
FIG. 4a.   Case IV.   22.1.23.
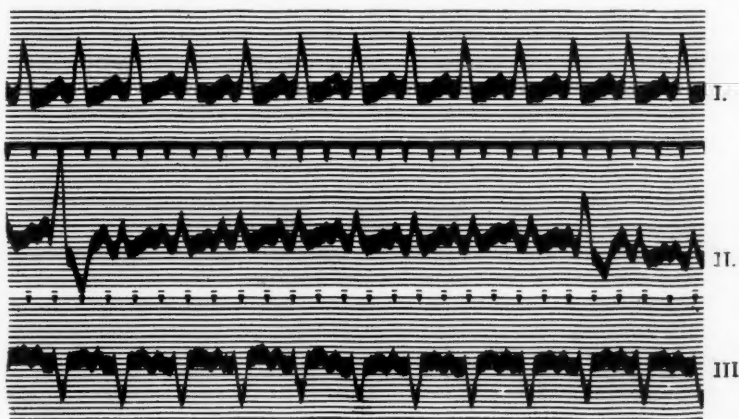
FIG. 4b.   Case IV.   20.7.23.   (Scale 0·2 sec.)
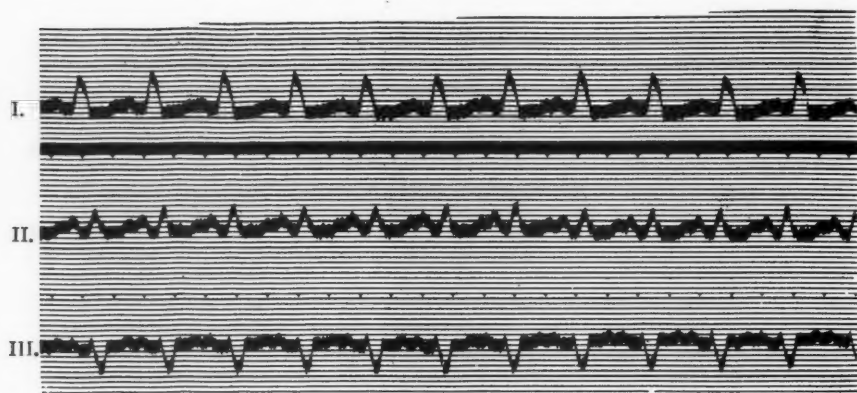
FIG. 4c.   Case IV.   14.4.24.   (Scale 0·2 sec.)
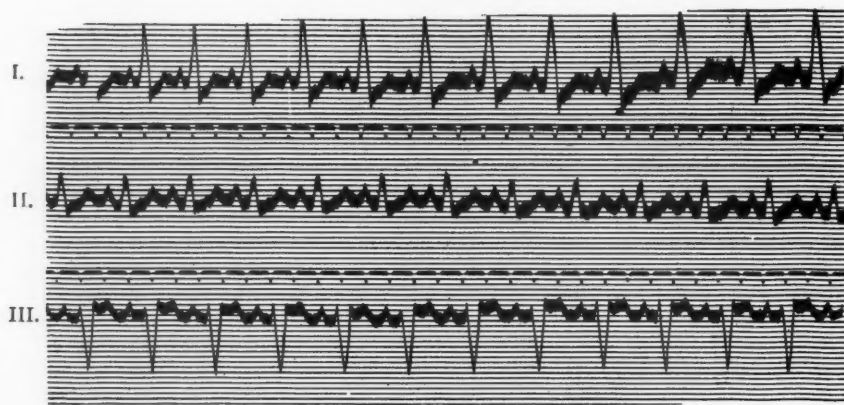
FIG. 4d.   Case IV.   18.1.26.   (Scale 0·2 sec.)
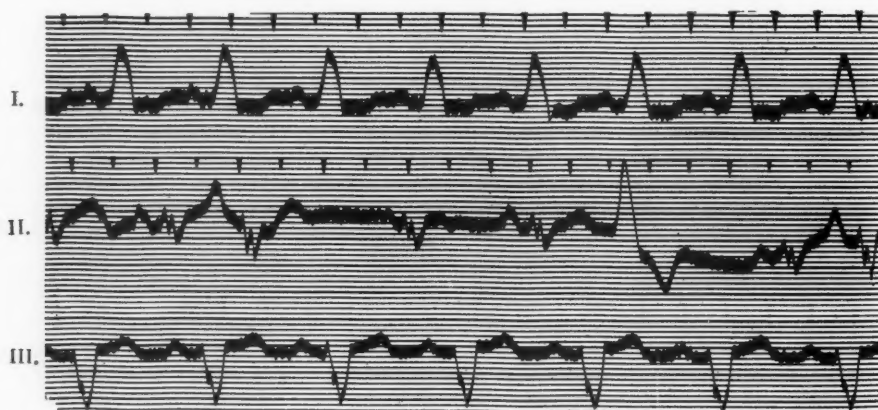
FIG. 4e.   Case IV.   26.10.28.   (Scale 0·2 sec.)
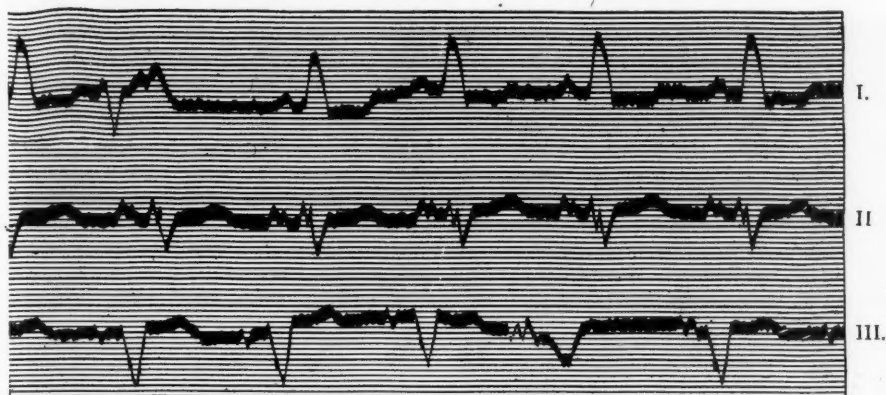
FIG. 4*f*.   Case IV.   17.12.28.
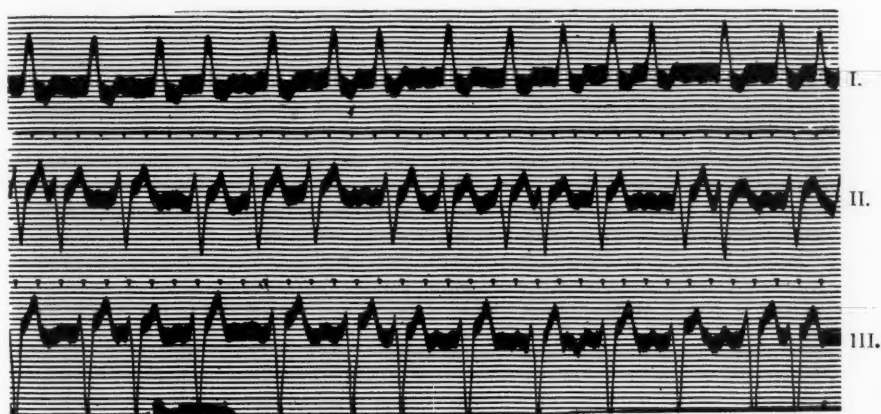
FIG. 5*c*.   Case V.   20 5 24.   (Scale 0·2 sec.)
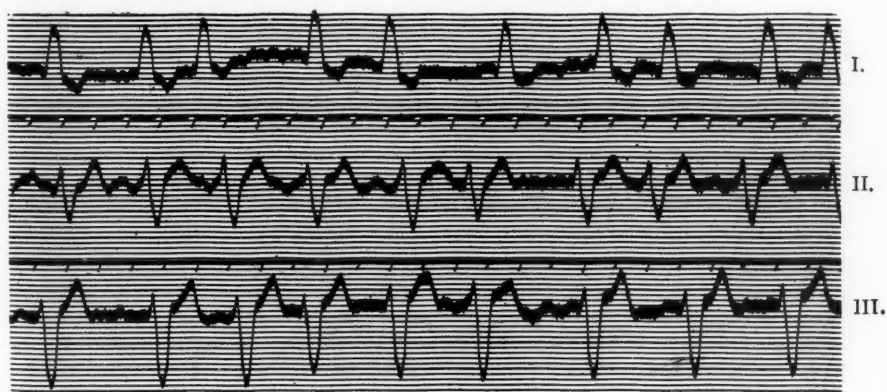
FIG. 5*d*.   Case V.   3.25, early.   (Scale 0·2 sec.)
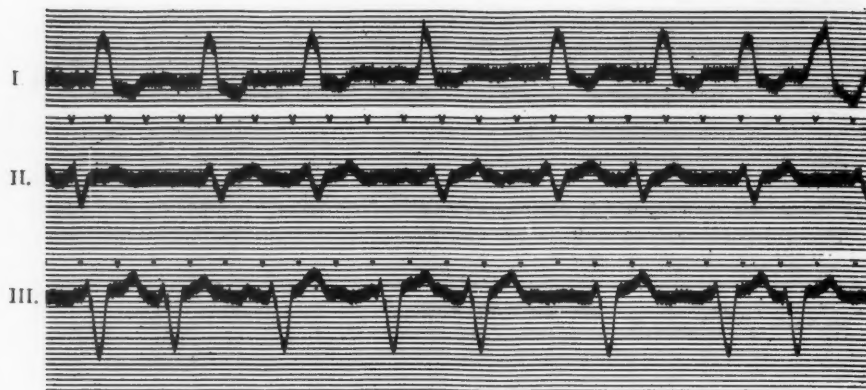
Fig. 5e. Case V. 1925, late. (Scale 0·2 sec.)
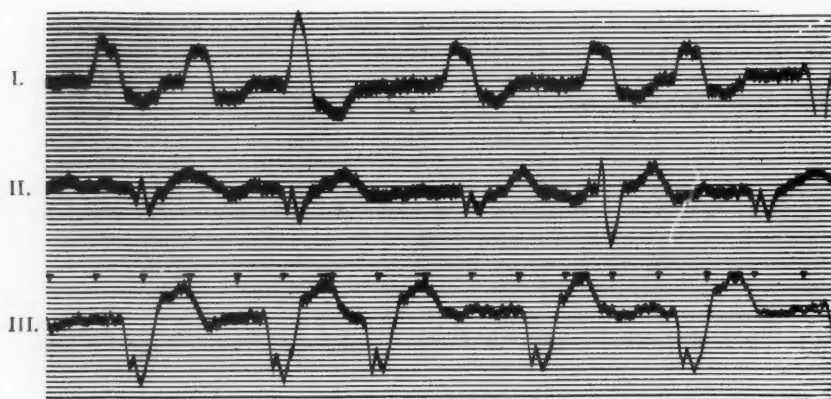
Fig. 5f. Case V. 1928, early. (Scale 0·2 sec.)
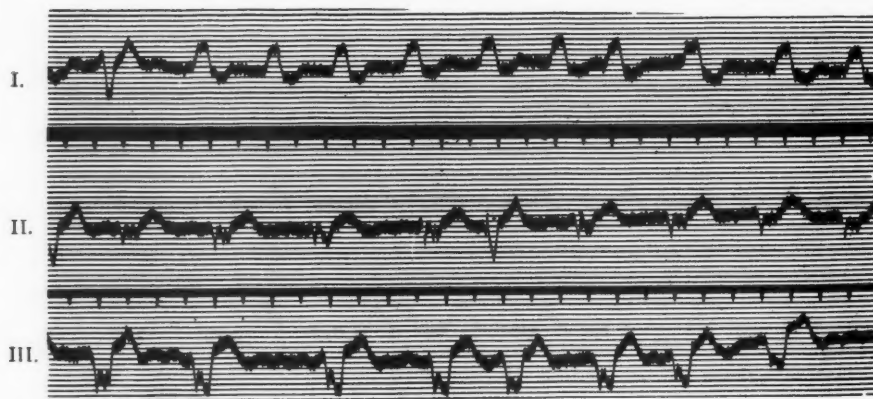
Fig. 5g. Case V. 1928, late. (Scale 0·2 sec.)
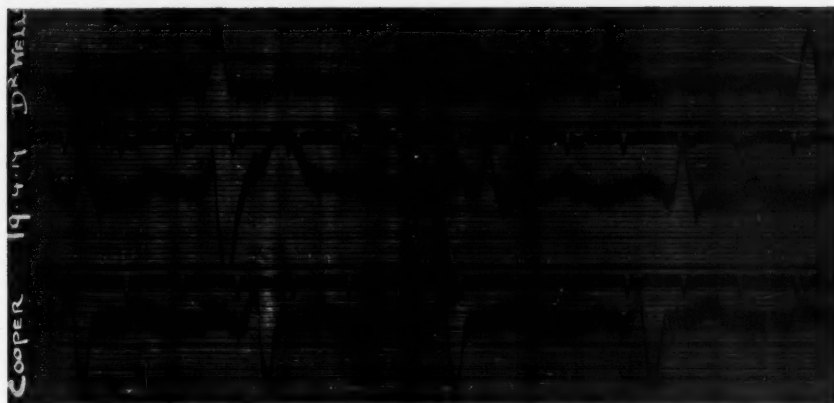
FIG. 5 *a*. Case V. 9. 4. 17. (Scale 0·2 sec.)

FIG. 5 *b*. Case V. 24. 4. 19. (Scale 0·2 sec.)

THE VENTRICULAR COMPLEXES IN MYOCARDIAL INFARCTION AND FIBROSIS [1]

By A. RAE GILCHRIST and W. T. RITCHIE

(From the University and the Royal Infirmary of Edinburgh)

AFTER injecting silver nitrate into the wall of the left ventricle or inter-ventricular septum (8, 14), crushing or cutting the apex of the heart (38), or ligating the coronary arteries and their branches (12, 15, 27, 31, 41, 42), the electrocardiograms may become transiently monophasic, the $R–T$ segment may become deviated from the iso-electric level or there may be negativity of T, which is greatest when the interference with the blood-supply of the left ventricle is most pronounced.

Since Herrick (19) recorded inversion of T I and T III in coronary thrombosis, many deformities of the ventricular complex have been described as following myocardial infarction, and in two cases (13, 20) after coronary ligation in man. The initial change observed by Pardee (32) was negativity of T I with fusion of R and T in leads II and III, namely $R–T$ deviation, which is synony-mous with the plateau type of curve described by Parkinson and Bedford (35), and the T en dôme of Clerc (8), and is in conformity with the abnormality of the ventricular complex following experimental ligation of the coronary blood-supply to the ventricular muscle. Pardee (33) subsequently considered the significant electrocardiographic feature of coronary arterial occlusion, whether sudden or gradual, to be ' the presence in one or more leads, usually in only one, of a downward sharply peaked T-wave with an upward convexity of the $S–T$ or $R–T$ interval'. This abnormality constitutes the coronary T-wave of Pardee, and the cove-plane T of Oppenheimer and Rothschild (30). A number of other deformities of the ventricular complex having been described as following myocardial infarction, it became evident that this was not associated with any one specific electrocardiographic deformity. Indeed, Wearn (45), from a study of ten cases, concluded that no one form of electrocardiogram was characteristic of myocardial infarction.

Not until serial records became available was the electrocardiographic evidence of myocardial infarction placed on a satisfactory basis. Although the literature on the subject is already voluminous, only one hundred and forty-eight cases have been reported in sufficient detail to permit of satisfactory analysis, the cases being those of Herrick (19) (1 case), Pardee (32, 34) (2 cases), Kahn (21) (2 cases), Wearn (45) (10 cases), Willius and Barnes (49) (9 cases),

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Clarke and Smith (7) (2 cases), Willius (47) (2 cases), Levine (24) (5 cases), de la Chapelle (6) (1 case), Wilson (51) (1 case), Bruce and Wilson (5) (1 case), Hamburger (18) (2 cases), Parkinson and Bedford (35) (28 cases), Stewart (44) (1 case), Moore and Campbell (29) (1 case), and Levine and Brown (25) (80 cases).[1]

In our analysis of these cases we have directed particular attention to: (1) the form of the ventricular complex, especially of the R–T segment and T; (2) the time interval elapsing between the acute attack and the registration of the electrocardiograms, and between the latter and the patient's death; (3) electrocardiograms recorded before the coronary syndrome; (4) the syndromal record, when available, and (5) the relation of the clinical diagnosis to the morbid anatomical lesion.

1. *The Ventricular Complex.*

(a) R–T deviation. Pardee's (32) observation that electrocardiograms taken within a week of the onset of infarction usually show deviation of the R–T segment from the iso-electric level has been confirmed and amplified by Parkinson and Bedford (35), who found some degree of R–T deviation in serial records of eighteen of their twenty-eight cases. The R–T deviation was most evident in leads I and III, elevation in lead I being constantly associated with depression in lead III, or vice versa. Both varieties of deviation were of about equal frequency. Further evidence was adduced of a positive R–T deviation being the precursor of a negative T in the same lead, whereas a negative deviation was subsequently and gradually replaced by a positive T. Parkinson and Bedford also pointed out that curves obtained a few weeks after the coronary syndrome conformed to one of two main types, T I type and T III type, according to the incidence of T inversion in leads I or III. A characteristic example of the T III type is that in Fig. 1, from a man aged 65, three months after sudden, intense, and prolonged pain in the xiphisternal region, radiating into both arms and relieved only by morphia. Thereafter he enjoyed excellent health and was capable of undertaking severe physical exertion until, two years later, he died of an acute empyema. In the course of time—it may be months or years—T slowly changes in the direction of normal, and even complete return to a normal upright T in each lead has been recorded.

Of the 148 cases now analysed 93 had records taken within ten days of the attack, and 52 had some degree of R–T or S–T deviation during that period. One of the cases, No. 68, presented the train of events in the evolution of the inverted T from the plateau type of curve as described by Parkinson and Bedford. In certain cases electrocardiograms in the early stages of the healing process are lacking, but subsequent records show definitely the later sequence of events in the evolution of T inversion. Even although control electrocardiograms and post-mortem confirmation of the clinical diagnosis be lacking, these

[1] These cases are grouped together in an Appendix at the end of this paper.

sequential alterations of the R–T segment and of T, occurring in the course of a short period of time, are strong presumptive evidence of myocardial infarction. A survey of this group of 148 cases confirms the general conclusions drawn by Parkinson and Bedford.
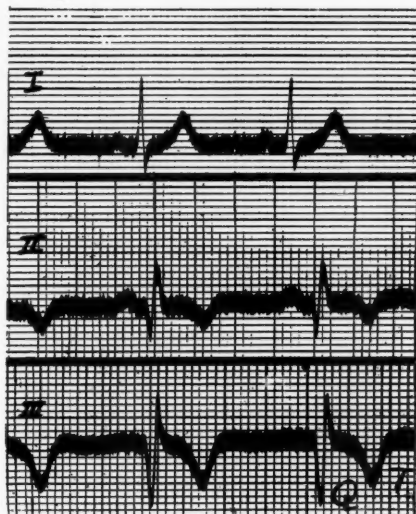
FIG. 1. Electrocardiogram from a man aged 65, three months after sudden intense and prolonged pain in the xiphisternal region. This is an example of the TIII type of curve described by Parkinson and Bedford (35).

Note the prominent Q wave in lead III.

Time-marker in this and similar electrocardiograms equals 0·04 second. Deflexion, 1 cm. equals 1 millivolt in all figures.

R–T deviation, however, whether positive or negative, is not an indubitable sign of myocardial infarction. It has been recorded during the course of rheumatic fever (9, 37) and in a study of X-ray therapy of rheumatic carditis (26). Distortion of the R–T segment has also been noted in the presence of pericardial effusion, both under clinical (40) and experimental conditions (23). In a case of acute rheumatic carditis, with slight inversion of TI, myocardial inflammation was found at autopsy (36). It may, therefore, be inferred that distortion of the R–T segment and of T, due to an organic lesion, depends on the site, not the nature, of the lesion, and that minute myocardial lesions may cause the distortion. It is, therefore, surprising that R–T deviation should not be observed at some stage of chronic dystrophic myocardial fibrosis accompanying gradual, as distinct from sudden, coronary occlusion, especially when we have evidence of T-negativity being not infrequent in those cases. Further observations, however, are needed to define the relation between the abnormalities of the ventricular complex and chronic disease of the myocardium.

Again, R–T deviation may occur apart from an organic lesion. In ventricular alternation of the frog's heart induced by subcutaneous injection of digitalis

or antiarin, the small alternation systoles, during which the apical portion
of the ventricle did not contract, yielded a ventricular complex with marked
$R-T$ fusion (3).   When a little more than half the lethal dose of digitalis had
been injected into the cat, T arose from S before the iso-electric level had been
reached (16).   Similar, if less fully developed, effects may be observed frequently
in man after the use of the drug (4, 10).   Pronounced $R-T$ deviation in the
perfused turtle's heart was recorded when the perfusion fluids were distinctly to
the alkaline side of normal, and the direction of T could be reversed by chang-
ing the reaction of the perfusate from acid to alkaline and vice versa ; R could
also be reversed (39).   Clinical electrocardiograms are also available when slight
change of pH of the blood might be expected. $R-T$ deviation was observed in
a case of uraemia four days before death, the $R-T$ segment being elevated in
leads I and II, depressed in III (52).   Lewis (28) found changes developing
in the $R-T$ segment as the degree of asphyxia and heart-block increased.   His
figure 138 shows marked $R-T$ deviation followed by a slightly negative T.   The
anoxaemia of heart failure in man may perhaps have similar, if less fully de-
veloped, effects on the electrocardiogram, for Greene and Gilbert (17) found
a decrease in the amplitude of T in men suddenly exposed to low oxygen
tensions in the inspired air, and sometimes T was diphasic.   Levine and Brown
(25) have noted distortion of the $R-T$ segment in lobar pneumonia.   Factors
such as the pH, anoxaemia, and digitalis therapy should, therefore, be borne in
mind in the interpretation of records taken after the onset of apparent
myocardial infarction.   Finally, accurate standardization of the galvano-
meter fibre is essential.   ' Over-shooting ' is a potent cause of distortion of the
curves, and this may well manifest itself in slurring and distortion of the $R-T$
segment.

Though $R-T$ or $S-T$ deviation is a frequent event in the early days after
infarction, there remains a number of cases in which records taken repeatedly
within ten days of the onset failed to reveal this abnormality.   Of the 148
cases analysed 93 had records taken within ten days of the onset, and 41 of
these, either under single or repeated examinations, failed to show $R-T$ devia-
tion.   It might be assumed that the presence or absence of this abnormality
depended on the particular site or extent of the lesion in the heart-muscle, and
that lesions involving the apex of the left ventricle favoured $R-T$ deviation.
These assumptions cannot yet be substantiated, because detailed post-mortem
examinations have been reported in only fifteen of these forty-one cases.

(b) T is the least stable feature of the electrocardiogram—its form, height,
and direction being influenced by many factors, even in health.   Exercise and
emotion, heat and cold, various chemical agents, and notably digitalis, are known
to affect it.   It may be influenced by the course and spread of the excitation
wave through the ventricles, for variations of the QRS group may be followed
by changes of T.   In some of the cases recorded as coronary occlusion the
inversion of T is associated with, and was doubtless due to, left ventricular
preponderance alone.   Further, inversion of T may be a transient event, for an

extra-systole may influence the form of T in the succeeding beat. An example is shown in Fig. 2. The patient was a female, aged 24, suffering from rheumatic fever. T is upright in the complex following the extra-systole, whereas in the other normal beats T is negative. The record in Fig. 3 is from a male, aged 57, presenting a right bundle branch defect. In the first post-extra-systolic complex, which has normal initial ventricular deflexions, T is inverted. We have not observed such alterations of T to persist for more than one heart-beat, but it is possible that negativity of T might persist for a number of beats and yet still be due to a functional defect in the ventricular muscle.

FIG. 2. Electrocardiogram from a female aged 24, suffering from rheumatic fever. An extra-systole (*ExS*) apparently influences the form of the *T*-wave in the first succeeding normal beat. *T* is upright in the complex following the extra-systole, whereas in the remaining complexes *T* is negative. In this and similar electrocardiograms the time-marker registers 28-57 vibrations per second.

FIG. 3. Electrocardiogram from a male, aged 57, presenting a right bundle branch defect. There is a transient change in the form of the *T*-wave in the first post-extra-systolic complex. In lead III the complex immediately after the extra-systole (*ExS*) is of normal outline with an inverted *T*-wave. The remaining complexes are of the type associated with a bundle branch defect and have upright *T*-waves.

Inversion of T in one or more leads may be observed in cases of angina pectoris that have never presented the coronary syndrome. Pardee's (33) analysis of cases and conclusions drawn therefrom are strictly in keeping with this statement. An example is shown in Fig. 4 from a man aged 51 who for eighteen months had been unable to walk more than thirty yards without suffering from constriction of the chest. Inversion of T in two leads may also be observed in patients who have never suffered from cardiac pain. For

example, TII and TIII were persistently inverted over a period of many months in a man aged 44, suffering from diabetes mellitus, whose arteries were greatly thickened, and in whom the blood-pressure reading was 210/130 (Fig. 5).
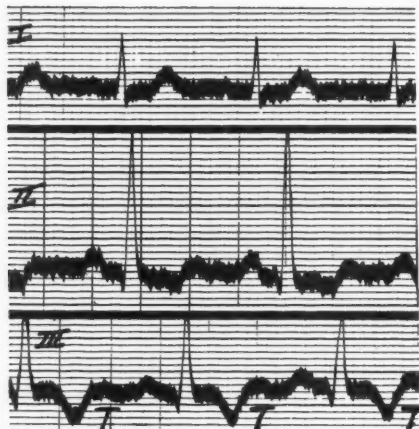
FIG. 4.   Electrocardiograms from a male aged 51, who, for eighteen months, had suffered from a sense of constriction in the chest on walking 30 yards.   He had had no pain.   Note the sharp inversion of T III.
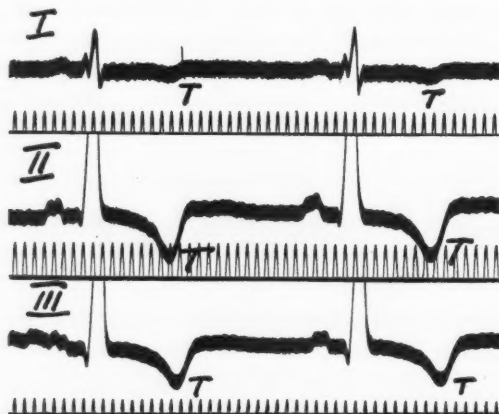
FIG. 5.   Electrocardiogram from a male aged 44, who had never experienced cardiac pain. He suffered from diabetes mellitus, high blood-pressure, and arteriosclerosis. T II and T III are markedly inverted.

All grades of coronary occlusion may occur between chronic progressive occlusion, with anginal pain and other chronic manifestations of myocardial ischaemia, and acute thrombosis with perhaps sudden death.   Coronary thrombosis is merely one, and perhaps a terminal, event in the course of chronic progressive disease of the heart.   Electrocardiographic abnormalities may have been present before thrombosis and infarction develop; subsequent alterations

in the form or direction of T may be manifestations of dystrophic myocardial fibrosis consequent on chronic arterial occlusion, and are not necessarily due to a myocardial infarct or to the reparative process in and around it. Although the basis for a diagnosis of coronary sclerosis is neither easy nor convincing, electrocardiographic abnormalities, particularly those affecting the form and direction of T in one or more leads, have, however, been recorded frequently in this disease. Willius and Brown (50) found that 17 of 25 cases of coronary sclerosis confirmed by necropsy had inversion of T, most commonly in lead I alone; and of 130 cases in which electrocardiograms showed negativity of T, other than in lead III alone, and in which necropsy was performed, significant coronary sclerosis was demonstrable in 52 cases (48). In 46 of these cases this abnormality was present only in lead I, in 32 cases in leads II and III, in 27 in leads I and II, and in 25 cases in all three leads. The fact that almost twice as many subjects had negativity of T in lead I alone, as compared with those who had negativity of T in all three leads, may perhaps indicate that the former group came under observation at a comparatively early stage of the disease, and that negativity of T in other leads too may be anticipated when the myocardial fibrosis is more advanced. In a chronic, progressive disease, negativity of T would probably not develop simultaneously in all three leads. In coronary sclerosis, apart from thrombosis, serial records may, therefore, be expected to show, over a period of months or years, gradual and progressive alterations of the ventricular complex, such as have been recorded by Cowan (11). But such alterations, whether or not they conform with those following myocardial infarction, are not indubitable evidence of such a lesion having occurred.

In the following case the interpretation of abrupt changes in the form of T is controlled by post-mortem observation.

A male, aged 57, admitted to Professor Murray Lyon's ward in October 1926, gave a history of shortness of breath and praecordial pain on exertion for three months, and of swelling of the ankles for a week. The heart was enlarged, the aortic valve was incompetent, and the Wassermann reaction of the blood was positive. Congestive heart failure rapidly subsided with rest in bed. He had several mild anginal attacks and occasional nocturnal dyspnoea while in hospital. He received no digitalis or strophanthin. Fourteen months later, there having been no unusually severe attacks of pain or dyspnoea, he was readmitted on December 29, 1927, when physical examination revealed no change in the state of the heart. On the morning of January 24, 1928, while walking towards his bed, about 7 a.m., he was suddenly seized with agonizing pain in the epigastrium, accompanied by great breathlessness and collapse. The pain radiated down both arms and over the front of the chest. The heart started 'going like a train', and ten minutes later it stopped suddenly 'with a pause and then a big beat and the fluttering feeling was away'. The pain, however, continued for some hours, less severe in character, but distressing in the extreme. He had two further attacks of tachycardia in rapid succession at 8.20 a.m. and at 9.40 a.m. on the same morning, and during these he suffered agonizing pain, with great prostration. In the third attack he was pale, cyanosed, and gasping for breath; the heart's rate was then 200 per minute. On each occasion the paroxysmal tachycardia lasted for about ten minutes, and its cessation brought considerable relief. Thereafter he experienced nine further

attacks, generally in the early morning or late at night. They were, however, of shorter duration than the earlier ones. The leucocyte count varied from 6,800 per c.mm. immediately after the first attack to 9,000 a few days later. The blood-pressure fell from 130/36 before the onset of the angina to 100/? in the interval between the attacks of paroxysmal tachycardia. Pericardial friction was never heard, there was no suppression of urine, congestive heart failure did not reappear after the first painful seizure, and the temperature remained afebrile. Extra-systoles were of frequent occurrence; they were often of nodal, occasionally of ventricular, origin. The patient died during an acute paroxysmal attack on the morning of February 2, 1928.

The post-mortem examination, made by Dr. R. D. Mackenzie, revealed a grossly hypertrophied and dilated heart. The aorta showed marked atheroma with calcification and the small depressed scars and striations of syphilitic aortitis. The aortic cusps were thick and calcified. The orifice of the right coronary artery was almost completely occluded by atheroma, and would admit only the point of a small pin. Beyond the constriction, the artery was of average size, but the wall was involved in a patchy atheroma. The left coronary orifice was of normal size and the early part of the artery showed a few scanty patches of atheroma. Dissection of both vessels to their finest branches revealed no evidence of thrombus formation, and no sign of infarction of the heart-muscle was discovered either macroscopically or in repeated microscopic sections. There was slight increase of the interstitial connective tissue in places, particularly in the inter-ventricular septum and on the posterior wall of the right ventricle. The artery to the auriculo-ventricular node was sclerosed but patent throughout.

The electrocardiogram recorded in October 1926 (Fig. 6) showed decided left-sided preponderance, with negativity of T II and T III, and a small diphasic T I. The initial ventricular deflexions in lead III were well formed and sharply cut. On January 4, 1928, there was S–T depression in lead I and T was slightly upright. S I had become more marked, S II less marked, and T II less negative than formerly. In lead III the initial ventricular deflexions had become small, slurred, and splintered, and varied in form with respiration. T III, formerly negative, was faintly positive and varied slightly from beat to beat according to the form of the preceding QRS group. The P-R interval measured 0·21 second (Fig. 7). In electrocardiograms taken at 10.15 a.m. on January 24, 1928, three hours after the onset of agonizing pain, T I was more definitively positive than previously, S–T was still slightly depressed, T II was more sharply negative, and resembled T of the first record taken thirteen months previously. The most marked change was the sharply pointed and inverted T III preceded by elevation of the S–T segment. There was a further degree of partial heart-block, for the P–R interval was now 0·24 second (Fig. 8). Fig. 9, obtained during a severe attack on January 25, 1928, showed complexes resembling those of the antecedent nodal extra-systoles and is therefore interpreted as paroxysmal tachycardia of a.-v. nodal origin. Leads II and III only were recorded, the tachycardia having ended before lead I was photographed. The last of the serial electrocardiograms (Fig. 10) was recorded twenty-three hours before death. In lead I there was less rounding and depression of the S–T interval, while T remained positive; the negativity of T II and T III had decreased.

(6)

(7)

(8)

(9)
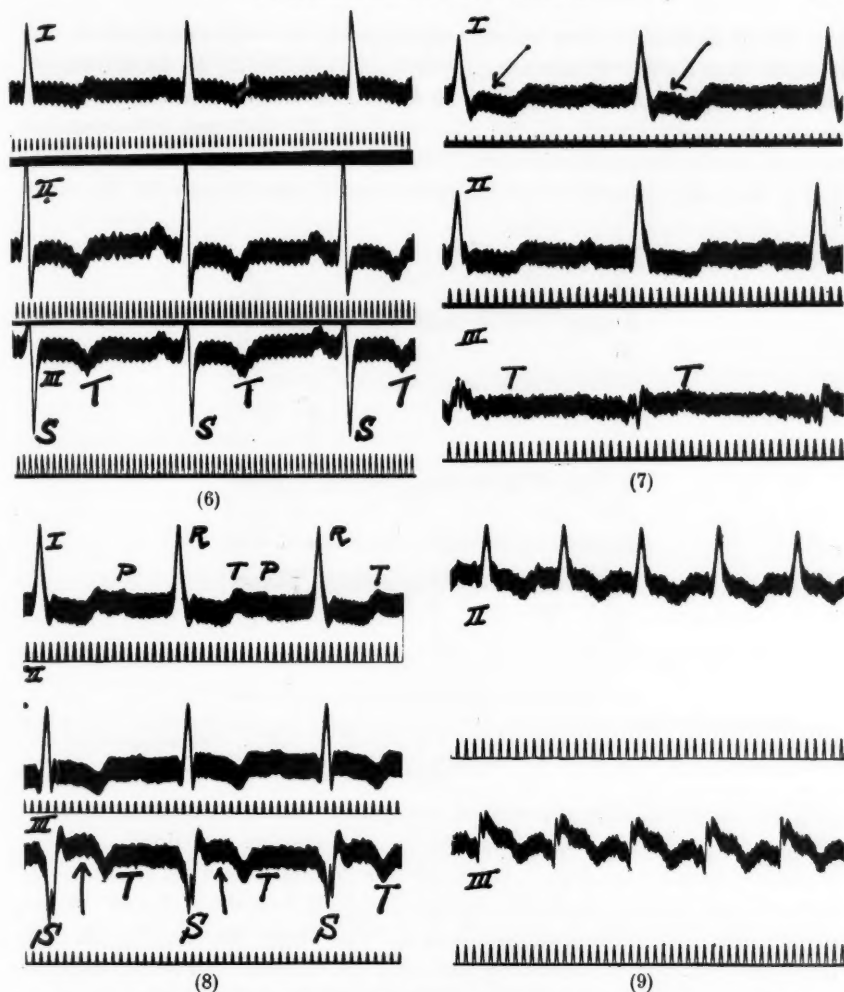
FIGS. 6, 7, 8, 9, 10. Serial electrocardiograms from a male aged 57, who suffered from severe anginal attacks associated with paroxysmal tachycardia. There was no thrombosis or infarction found at post-mortem examination. For clinical history, see p. 279.

FIG. 6 :—Recorded October 1926, shows the presence of a left-sided preponderance. *T* I is diphasic. *T* II and *T* III *are sharply inverted and associated with slight rounding of the S–T segment*. In lead III the deflexions are well formed and sharply cut. The *P–R* interval measures 0·17 seconds.

FIG. 7 :—Recorded on January 4, 1928, before the onset of severe anginal attacks, shows a change in the form of the complexes in all leads particularly affecting lead III. There is slight depression of the *S–T* interval in lead I. *T* II is blunter than formerly ; *T* III, *formerly negative, is now positive*, and is preceded by a small splintered and slurred complex. The *P–R* interval measures 0·21 seconds.

FIG. 8 :—Recorded on January 24, 1928, three hours after the onset of agonizing anginal pain. A further change has taken place in all three leads. Slight depression of the *S–T* interval is still present in lead I. *T* II is more sharply negative. *T* III *has reverted to a sharply pointed negative form, and is now preceded by definite elevation of the S–T segment*. There is also a change in the form of the initial deflexions in lead III. The *P–R* interval is extended to 0·24 second.

FIG. 9 :—Recorded on January 25, 1928, during a severe anginal attack, shows complexes resembling those of previously observed nodal extra-systoles. The rate is 187 per minute, and the record is interpreted as paroxysmal tachycardia of a.-v. nodal origin. Leads II and III only were photographed.

The Q deflexion. Low voltage of the initial ventricular deflexions was recorded in a number of cases, e. g. Nos. 3, 5, 7, 9, 10, 11, 23, 28, 42, 46, 49, 55, and 64. Prominence of Q is to be noted in seventeen cases (Nos. 37, 39, 56, 57, 60, 61, 62, 82, 95, 96, 107, 114, 120, 123, 128, 132, and 147) occurring as early as the fourth day in cases Nos. 61 and 62. In the latter case Q was 8 mm. deep eight months after the syndrome, whereas in case 60 the depth
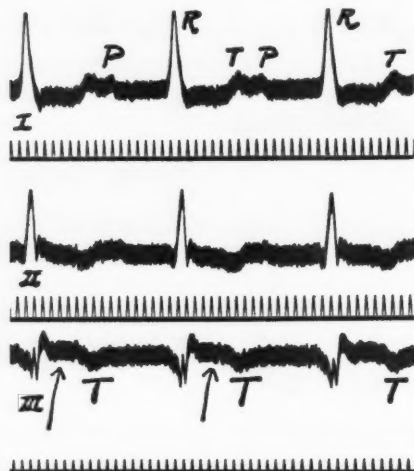
Fig. 10:—Recorded on February 1, 1929, twenty-three hours before death. This record shows less rounding and depression of the S-T interval in lead I. The negativity of T in leads II and III has decreased. S-T elevation is still present in lead III.

of Q had decreased after a period of two years. Of these seventeen cases the presence of an infarct was confirmed by post-mortem examination in two instances (cases 82 and 147). The depth of a normal Q does not exceed 2 mm. In four cases we have observed the depth of Q III to be 3, 6, 9, and 10 mm. respectively. The abnormality is seen in Fig. 1 and also in Fig. 11. The latter was recorded in a seafaring man, aged 49, who had suffered from angina pectoris ten years previously, but had subsequently led an active, strenuous life until, two weeks before the record in Fig. 11 was taken, he experienced severe pain and constriction of the chest for some hours, followed by praecordial pain on effort.

(2) *Further Considerations.*

The time interval between the taking of the record and the death of the patient has to be considered before deciding whether deformity of the ventricular complex is significant of myocardial infarction. Almost any electrocardiographic abnormality may be recorded at, or shortly before, death. Figure 4 of Kahn and Goldstein's paper (22) depicts R-T deviation twelve hours before death in a case of arteriosclerosis and diabetic gangrene. Fig. 12 is a record from a man, aged 67, who had been subject to attacks of angina pectoris for three

and a half years; if he walked fifty yards he had to halt until the praecordial pain subsided. Fig. 12 shows marked downward *S–T* deviation in leads II and III, but it was recorded only an hour and a half before the patient's death. The coronary arteries and their branches were atheromatous and extensively calcified; throughout the left ventricle there were large patches of chronic interstitial myocarditis, but there was neither thrombosis nor infarction.
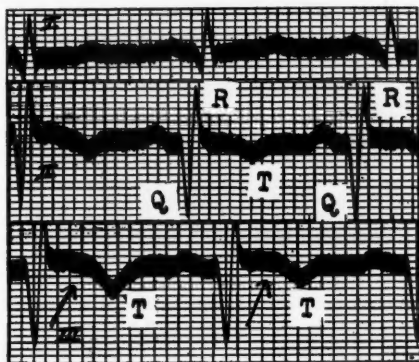
FIG. 11. Electrocardiograms from a male aged 49. *R–T* elevation is present in leads II and III after an attack of severe pain and constriction in the chest. Note the presence of prominent *Q*-waves in leads II and III.
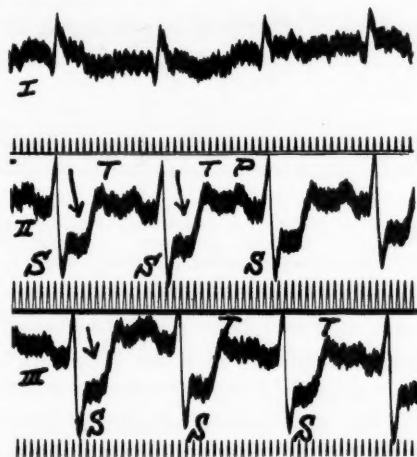
FIG. 12. Electrocardiograms from a male aged 67, who had been subject to anginal attacks for 3½ years. This record was made only 1½ hours before the patient's death. There was no coronary thrombosis or myocardial infarction found at autopsy, though pronounced *S–T* depression is present in leads II and III.

Again, as a terminal event, *T* may be inverted in all three leads although the patient never suffered from angina pectoris nor presented the coronary syndrome, as in the case of a man, aged 67, affected with syphilitic cirrhosis of the liver and presenting bradycardia at a rate of 28–34 per minute. Fig. 13

was recorded the day before that patient's death : none of the coronary arteries were occluded and there was no myocardial infarct. We are, therefore, unable to accept a diagnosis of myocardial infarction that is based solely on terminal or agonal electrocardiograms.
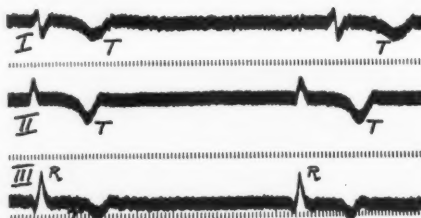
FIG. 13. Electrocardiogram from a male aged 67, recorded the day before death. The *T*-waves are inverted in all three leads and *T* I and *T* II are each preceded by slight rounding of the *S–T* interval. The ventricular rate varied from 28–34 per minute. The man suffered from syphilitic cirrhosis of the liver. There was no coronary occlusion or myocardial infarction.
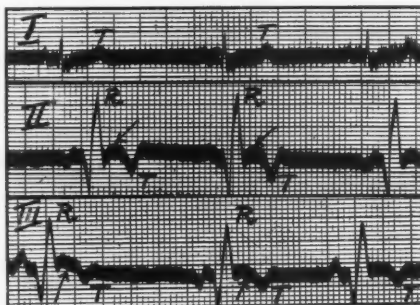
FIG. 14. Electrocardiogram from Case I, a female aged 57, four weeks after an attack of coronary thrombosis. The initial ventricular deflexions are prolonged in leads II and III to 0·16 second. *T* II and *T* III are sharply inverted. *T* II is preceded by rounding of the *R–T* segment, and *T* III by elevation of the *R–T* segment.

In the whole series reviewed there are only sixteen cases with control presyndromal electrocardiograms, and in eleven *T* was originally positive in all leads. In three of these cases (Nos. 63, 100, 123) the *T* waves, before and after the infarction, were of the same upward direction. Five cases (Nos. 35, 76, 86, 109, 140) had inversion of *T* in one lead before the attack, and in two cases (Nos. 86, 109) similar *T*-waves were recorded after the attack. After the syndrome only four cases (Nos. 29, 76, 140, 146) showed a change in the direction of the *T* waves, affecting two or more leads.

In five cases records were taken during the period of the coronary syndrome. In two (Nos. 23 and 26) *T* was positive in all three leads, in one (No. 20) there was *R–T* deviation, in one (No. 18) *T* was negative in all three leads, in one (No. 21) *T* II and *T* III were negative.

Anatomical Evidence with Two Case Reports.

Post-mortem records are available in only 44 of the 148 cases. To these we now add two new cases.

Case I. When a woman, aged 57, was admitted to hospital four weeks after a sudden paroxysm of intense epigastric pain she was somewhat delirious, the lower limbs were dropsical, the face was ashen-grey, the skin cold, the temperature afebrile, the pulse barely perceptible, the breathing shallow, the sputum haemorrhagic. She died four days later. In Fig. 14 taken on the day of death, the initial ventricular deflexions in leads II and III are prolonged to 0·16 second; *T* II and *T* III are inverted; *T* II is preceded by an upward convexity of the curve, and *T* III by elevation of the *R–T* segment.

The post-mortem examination was made by Dr. R. Carmichael. Both coronary arteries and their branches presented marked atheroma with pronounced narrowing of the lumen of the vessels. The anterior descending branch of the left coronary artery was calcareous and, three inches from its origin, was occluded by a firm, greyish ante-mortem thrombus which extended into the more distal portion of the artery and its branches. The apical third of the heart-wall was the seat of a large infarct, and as a result of the necrosis of the apical portion of the interventricular septum there was an orifice through which a finger could be passed (Fig. 15). The outer wall of the heart near the apex consisted of three zones of approximately equal thickness.

(1) An outer layer, just under the pericardium, consisted of a young cellular connective tissue containing numerous large mononuclear cells and fibroblasts. Lymphocytes were present in considerable number about the blood-vessels, and a few of these cells were found infiltrating the tissues.

(2) A middle layer of well-formed fibrous tissue containing sparse adult connective tissue cells and a few hypertrophic muscle-fibres.

(3) A subendocardial layer of necrotic muscle-fibres.

The myocardium of the left ventricle elsewhere showed chronic interstitial myocarditis. The myocardium of the right ventricle was largely replaced by fibrous tissue and fat. There was very marked thickening of the intima of many of the small branches of the coronary vessels, particularly in the region of the apex.

The scanty number of autopsies is particularly disappointing because an autopsy would have been most valuable in certain cases which had been subjected to careful and prolonged electrocardiographic study. The abnormalities of the ventricular complex have usually been associated with thrombosis of the left coronary artery or its branches. The degree of coronary anastomoses and the rôle of the Thebesian vessels in maintaining an adequate circulation through the ventricular muscle may, however, be important factors in determining whether sudden coronary occlusion will be followed by myocardial infarction (46). Parkinson and Bedford (35) conclude that the size and site of the infarct and its relation to the apex, rather than the particular artery occluded, may determine whether the inversion is to be of the *T* I type or *T* III type. Barnes (1), however, considers that the *T* I type is related to infarction of the anterior surface of the left ventricle and apex, the *T* III type to infarction of the posterior surface of the left ventricle, with or without apical infarction.
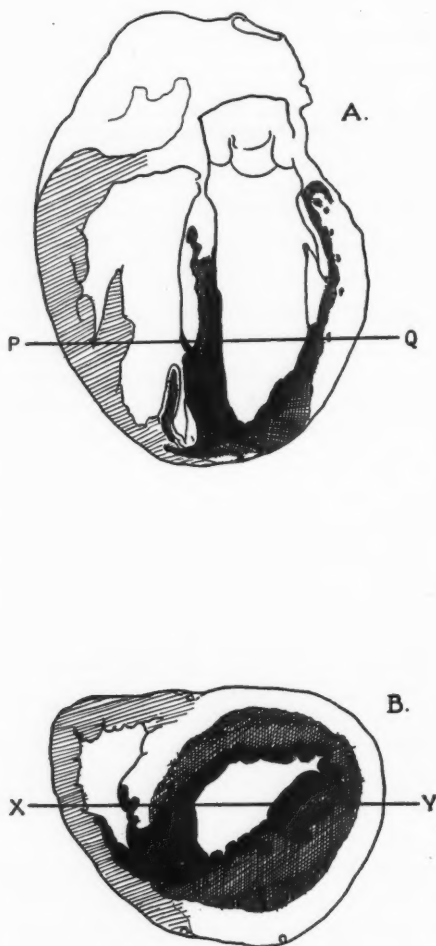
FIG. 15.   Diagram of the site of the pathological changes found in the heart of Case I.

Black—Indicates necrotic heart-muscle.
Cross Hatching—Indicates complete replacement of muscle by fibrous tissue.
Light Shading—Indicates partial replacement of heart-muscle by fibrous tissue
and fat.   This area contains numerous small (microscopic) bundles of fairly
healthy muscle, but the greater part of the muscular tissue in this region
has disappeared as a result of a very extensive fatty infiltration.   There is
also a certain amount of ' chronic interstitial myocarditis ' here.
Unshaded—Heart-muscle—this is moderately healthy.
In diagram A the line P-Q indicates the plane of diagram B.
In diagram B the line X-Y indicates the plane of diagram A.

Of the total post-mortem examinations, forty-four in number, there are ten (Nos. 21, 25, 33, 49, 65, 66, 97, 98, 112, 113) in which the infarct is described as involving the anterior or posterior wall of the left ventricle. There are three cases (Nos. 21, 33, 113) in which the infarct was found in the anterior wall. Case 21 may be excluded on account of a lesion of the right bundle branch. In the remaining two cases, the curves conform to the type associated with an anterior distribution of the infarct as described by Barnes. Such an agreement, however, is lacking in the series of seven cases (Nos. 25, 49, 65, 66 97, 98, 112) in which autopsies showed that the posterior wall of the left ventricle was infarcted. Case 66 may be disregarded on account of left bundle branch block. Case 97 agrees with the type of distortion predicted by Barnes. The remaining cases do not conform to the type of distortion anticipated. For example, in case No. 65 there was found a recent yellow infarct of the posterior wall of the left ventricle and papillary muscles of the mitral valve. R–T elevation occurred in leads I and II six days after the attack and fifteen days before death. Now this is the type of distortion which, it is suggested, tends to accompany a lesion of the anterior wall of the ventricle. We are of opinion that, until further evidence has been acquired, the form of the electrocardiographic distortion cannot be regarded as a definite localizing sign of the infarct.

It is not without significance, however, that in a recent study Barnes and Whitten (2) found that 84 per cent. of patients with predominant strain on the left ventricle had inversion of the T wave in lead I or in leads I and II. They point out that this is also the type of distortion which they associate with infarction of the anterior surface and apex of the left ventricle. On the other hand, they believe that strain predominating on the right ventricle produces negativity of T in leads II and III. None of their patients in this group had inversion of the T wave in lead I or in leads I and II. Just as this combination of changes may be found in the presence of predominating right-sided strain, so also may it be seen in patients recovering from infarction of the posterior surface and apex of the heart. These findings are important in the interpretation of electrocardiograms after an alleged attack of coronary thrombosis. Further work may well substantiate the validity of the conclusions of these workers. In the meantime, the available evidence lends support to the view that an isolated electrocardiogram showing merely an inversion of the T waves in certain combinations of leads cannot be held in itself to substantiate a diagnosis of previous infarction, strain or infarction apparently producing at times virtually identical changes.

Detailed post-mortem reports are available in eighteen cases in which R–T deviation had been observed. In case No. 3 the deviation was not observed until 115 days after the infarction, six days before death; in case No. 4 there was R–T deviation in lead I, thirty-nine days after the seizure, and in all three leads eighty-four days later, the day before death. In both these cases the apex of the left ventricle presented a thin-walled aneurysmal dilatation,

with partial obstruction of calcareous coronary arteries in case No. 3, and complete occlusion of the anterior descending branch of the left coronary artery in case No. 4. In case No. 19 there was $R-T$ deviation sixty-seven days after the attack ; a large aneurysm of the left ventricle was found, and an old thrombus occluded the descending branch of the left coronary. In case No. 25 there was reciprocal $R-T$ and $S-T$ deviation in leads I and III eighteen hours before death ; the left coronary artery was partially occluded, a small branch was thrombosed, and near the apex was a small area of necrosis. In case No. 33 one electrocardiogram, taken ten days after the onset of the coronary syndrome and a few hours before death, showed a deviation, positive in lead I and negative in lead III. The left ventricle had ruptured after infarction, the result of thrombosis of the left coronary artery. In case No. 65 there was positive $R-T$ deviation in leads I and II six days after coronary thrombosis, a fortnight before death. A recent infarct involved the posterior wall of the left ventricle, margo obtusus and papillary muscles of the left ventricle, with stenosis and thrombosis of the left circumflex artery. Case No. 72 showed the TI type of deviation of the $R-T$ segment ten days after the thrombotic attack. The electrocardiogram was made on the day of death and the subsequent post-mortem revealed an infarct of the left ventricle and inter-ventricular septum, the result of occlusion of the descending branch of left coronary artery. In case No. 75 the post-mortem findings were apparently similar to those in case 72, but $S-T$ depression was present in lead I. In the remaining cases (Nos. 82, 84, 88, 90, 97, 98, 141, 143) it is not possible to correlate accurately the electrocardiographic distortion with the post-mortem findings, as the exact site of the infarction is not always stated.

So far as we can discover, there have been no cases reported in which the remarkable sequence of events in the evolution of the ' coronary T ' from $R-T$ deviation has been followed by post-mortem studies of the heart. The two that conform most closely are cases Nos. 53 and 90. Case 53 had slight $R-T$ deviation in lead II four days after the onset of coronary thrombosis and inversion of TII and TIII sixteen and eighteen months later. Twenty-two months after the thrombosis an old fibrous infarct was found in the inter-ventricular septum, anterior wall of left ventricle and apex. Case 90 was observed for twenty-seven months. From five to ten days after the attack positive deviation of the $R-T$ segment was found in leads II and III. This was followed by negativity of T in all leads thirty-six days after the attack. Seventy days later TIII was positive, TI and TII still negative, and twenty-seven months from the onset TI, II, and III were each positive. The patient died five months after the last record, and the post-mortem showed complete occlusion of the descending branch of the left coronary artery, aneurysm of the apical portion of the left ventricle, and a mural thrombus within the aneurysm.

Post-mortem examinations have been reported in detail in only fifteen of the forty-one cases in which records taken within ten days of the onset failed to reveal $R-T$ deviation. In four (Nos. 10, 15, 21, 67) of these fifteen

cases the inter-ventricular septum was involved in the infarction. Thrombosis involving the circumflex artery is reported in two instances (Cases 67, 69). There does not appear to be any characteristic pathological finding which would distinguish this group of post-mortem cases from that in which deviation of the *R–T* segment was found.

FIG. 16. Electrocardiogram from Case II, a female aged 60, fifteen days after an attack of coronary thrombosis and two hours before death. The rate of the heart is 194 per minute, and the record is interpreted as paroxysmal ventricular tachycardia. (Lead II).
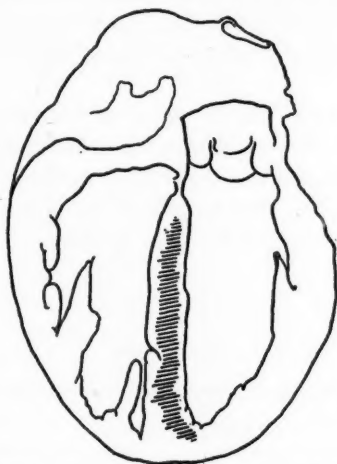
FIG. 17. Diagram of the heart from Case II. The shaded area indicates the extent of the infarct found in the interventricular septum.

The following case is an example of an infarct confined to the interventricular septum :

Case II. A woman, aged 60, while recovering from an attack of influenza, fell down and was probably unconscious for a few seconds. Ten minutes later she was found to be conscious, the face pale, yet cyanosed and bedewed with sweat; she was then extremely breathless and suffering from severe pain which passed through the middle of the chest into the back and both arms. The pain persisted for twenty-four hours. Eleven days later, while taking a gentle walk, she again became extremely breathless. On the following day she again 'felt queer' and fell forward on her bed. She was now deeply cyanosed, suffered from severe epigastric pain and nausea, and again broke into a cold sweat. When admitted to hospital two days later she was cyanosed, orthopnoeic, and pulseless, and complained of flatulence but not of pain. The ventricular rate varied from 160 to 190 per minute ; the heart-sounds had a tic-tac character; crepitations were audible at the bases of the lungs, but there was no sputum.

Electrocardiograms taken on the following day, two hours before the patient died, revealed ventricular paroxysmal tachycardia at a rate of 194 per minute (Fig. 16). At the autopsy, performed by Dr. R. Carmichael, the right coronary artery and its branches were found to be healthy, but the anterior descending branch of the left coronary artery was slightly atheromatous. The interventricular septum was the seat of a large recent infarct, which left only the extreme apical and basal portions of the septum unaffected (Fig. 17).

Conclusions.

A study of 148 cases with serial electrocardiograms indicates that sequential alterations of the $R-T$ segment and of T, occurring in the course of a short period of time, are strong presumptive evidence of myocardial infarction. Similar changes developing more slowly may be observed apart from myocardial infarction, and may be due to dystrophic myocardial fibrosis following chronic, progressive, coronary sclerosis. The evidence available at the present time does not lend support to the view that the form of the electrocardiographic distortion can be regarded as a definite localizing sign of the infarct.

Professor Murray Lyon kindly placed at our disposal one of the cases reported above. We are also indebted to Dr. R. Carmichael for his construction, from microscopical sections, of the diagrams illustrating pathological changes in the heart, shown in Fig. 15. The work has been done by one of us (A. R. G.) under the auspices of the Medical Research Council.

APPENDIX.

The 148 cases analysed in the foregoing communication are :—

Serial No.		Author's Case No.	Serial No.		Author's Case No.
1	Herrick (19)	1	24	Clarke and Smith (7)	2
2	Pardee (32)	1	25	,, ,,	4
3	Kahn (21)	2	26	Willius (47)	1
4	,,	3	27	,,	2
5	Wearn (45)	1	28	Levine (24)	1
6	,,	2	29	,,	2
7	,,	3	30	,,	3
8	,,	4	31	,,	4
9	,,	5	32	,,	5
10	,,	6	33	de la Chapelle (6)	3
11	,,	7	34	Wilson, W. J. (51)	1
12	,,	8	35	Bruce and Wilson, F. N. (5)	6
13	,,	9	36	Hamburger (18)	1
14	,,	10	37	,,	2
15	Willius and Barnes (49)	1	38	Pardee (34)	1
16	,, ,,	2	39	Parkinson and Bedford (35)	1
17	,, ,,	3	40	,, ,,	2
18	,, ,,	4	41	,, ,,	3
19	,, ,,	5	42	,, ,,	4
20	,, ,,	6	43	,, ,,	5
21	,, ,,	7	44	,, ,,	6
22	,, ,,	8	45	,, ,,	7
23	,, ,,	9	46	,, ,,	8

Serial No.			Author's Case No.	Serial No.			Author's Case No.
47	Parkinson and Bedford (35)		9	98	Levine and Brown (25)		37
48	,,	,,	10	99	,,	,,	39
49	,,	,,	11	100	,,	,,	40
50	,,	,,	12	101	,,	,,	41
51	,,	,,	13	102	,,	,,	42
52	,,	,,	14	103	,,	,,	50
53	,,	,,	15	104	,,	,,	51
54	,,	,,	16	105	,,	,,	52
55	,,	,,	17	106	,,	,,	54
56	,,	,,	18	107	,,	,,	55
57	,,	,,	19	108	,,	,,	56
58	,,	,,	20	109	,,	,,	58
59	,,	,,	21	110	,,	,,	61
60	,,	,,	22	111	,,	,,	62
61	,,	,,	23	112	,,	,,	63
62	,,	,,	24	113	,,	,,	64
63	,,	,,	25	114	,,	,,	65
64	,,	,,	26	115	,,	,,	66
65	,,	,,	27	116	,,	,,	67
66	,,	,,	28	117	,,	,,	69
67	Stewart (44)		1	118	,,	,,	72
68	Moore and Campbell (29)		1	119	,,	,,	80
69	Levine and Brown (25)		1	120	,,	,,	82
70	,,	,,	2	121	,,	,,	83
71	,,	,,	3	122	,,	,,	86
72	,,	,,	4	123	,,	,,	89
73	,,	,,	7	124	,,	,,	91
74	,,	,,	8	125	,,	,,	93
75	,,	,,	9	126	,,	,,	102
76	,,	,,	10	127	,,	,,	103
77	,,	,,	11	128	,,	,,	104
78	,,	,,	14	129	,,	,,	105
79	,,	,,	15	130	,,	,,	106
80	,,	,,	16	131	,,	,,	113
81	,,	,,	17	132	,,	,,	115
82	,,	,,	18	133	,,	,,	119
83	,,	,,	19	134	,,	,,	126
84	,,	,,	20	135	,,	,,	132
85	,,	,,	21	136	,,	,,	133
86	,,	,,	22	137	,,	,,	134
87	,,	,,	24	138	,,	,,	135
88	,,	,,	26	139	,,	,,	136
89	,,	,,	27	140	,,	,,	137
90	,,	,,	28	141	,,	,,	138
91	,,	,,	29	142	,,	,,	139
92	,,	,,	30	143	,,	,,	140
93	,,	,,	32	144	,,	,,	141
94	,,	,,	33	145	,,	,,	142
95	,,	,,	34	146	,,	,,	143
96	,,	,,	35	147	,,	,,	144
97	,,	,,	36	148	,,	,,	145

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FOUR CASES OF FIBROSIS OF THE MYOCARDIUM WITH ELECTROCARDIOGRAPHIC AND POST-MORTEM EXAMINATIONS [1]

By J. A. G. BURTON, JOHN COWAN, J. HUNTER KAY, A. J. MARSHALL, J. K. RENNIE, J. H. RAMAGE, and J. H. TEACHER.

THERE are, as yet, but few published records of cases of fibrosis of the myocardium with electrocardiographic and post-mortem examinations, and as it is important that such records should be numerous these four cases are reported in some detail.

Case I. The patient was an active clergyman. He died in February 1928 at the age of 63.

He had had many illnesses in adult life, pleurisy in 1890, influenza in 1896, enteric fever in 1903, hepatic colic in 1910, jaundice in 1915, recurrent attacks of hepatic colic followed by an operation for the removal of gall-stones in 1918. He was a very active man, and smoked heavily and drank large quantities of tea.

In the autumn of 1920 he felt run down, being easily tired, and off colour, but he continued at work. On the morning of 23.12.20 he went into the yard to saw some wood and, while at work, suddenly experienced pain in the chest, and felt very faint. He had to cease work at once and was just able to walk into his house, a few yards away, and then collapsed. When seen shortly afterwards he was lying on a sofa, extremely ill and collapsed, with a barely perceptible, irregular, pulse of about 40. After free stimulation he improved slowly. He was kept in bed for a month. When he was allowed to get up he found that he was very easily tired and incapable of much exertion, but he made steady progress, and, after six months' rest, he was able to resume his usual duties.

For the first time in his life he now paid some attention to his health, and he remained in full work, which he undertook without difficulty. In 1925 he undertook more arduous work, which entailed constant travelling all over the country. He continued in good health until the spring of 1927. At this time he 'caught cold' and became 'rather wheezy'. This troubled him all summer. In July he complained of a burning sensation, apparently painful, below the sternum, and in August noticed that this was definitely related to exertion. In September he had a severe attack of pain while hurrying to catch a steamer, and he had to stop walking at once though this entailed his 'losing the boat'. Attacks of pain now recurred frequently, always on exertion, and as the weeks passed the degree of exertion which produced pain became less and less. At first he had pain when walking up hill, but now pain might ensue when he was walking quietly on the flat. The pain was substernal in site, and sometimes radiated into the arms, as far as the elbows.

At the end of October he was sent to bed but he was never quite comfortable as he felt that the spasms were 'not far away'. His pulse remained quiet

and regular, about 65 per minute, with a blood-pressure of 140 mm. At the end of 1927 he improved and was allowed to get up for a little time each day. In January 1928 the improvement had continued, and he was able to take a warm bath without any discomfort. But on 1.2.28 he had a very severe attack of angina, and another on the night of 4/5.2. Next morning he looked pinched

28.1.21.   1.4.21.

15.9.25.   Fig. 1. Case I.   27.10.27.
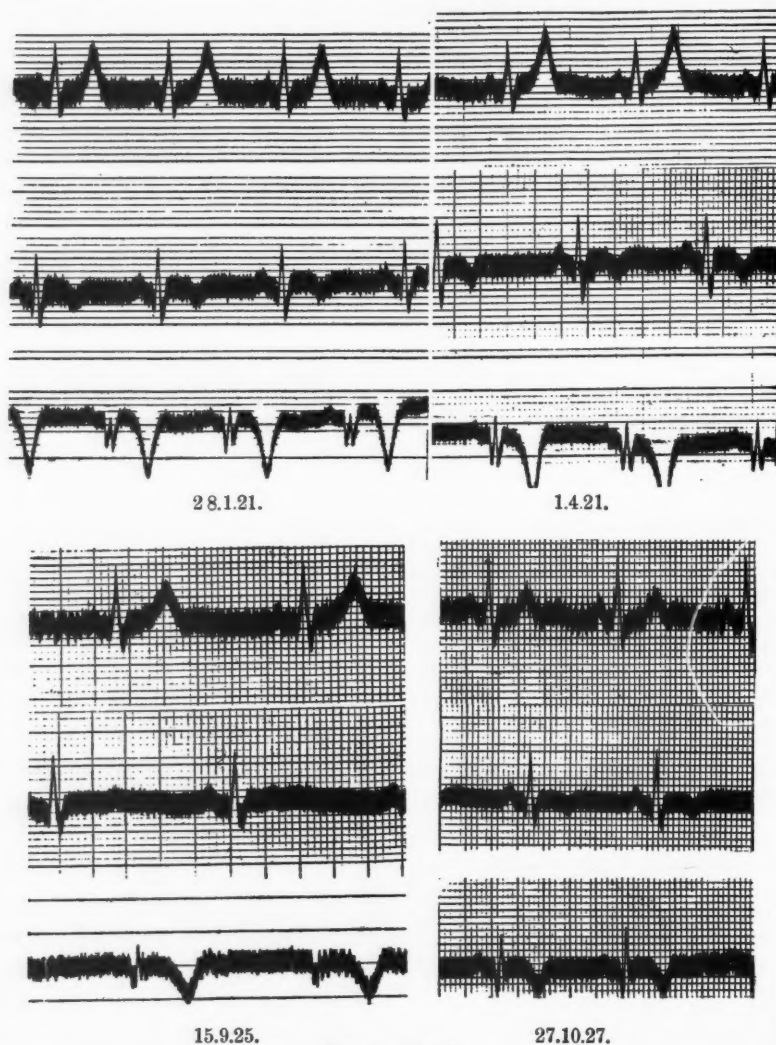
and pale; and his pulse was infrequent and feeble. He remained without discomfort until the morning of 8.2. He awoke very well and cheery, with an appetite, but, when finishing his breakfast, was again seized with severe pain, and died within five to ten minutes.

The condition of the heart varied but slightly through all these years. In 1.21 the apex impulse was situated in the fifth interspace, 14 cm. from mid-

sternum, and the area of dullness measured 14·5 cm. transversely.   The area of
hepatic dullness measured 12 cm. in the nipple line.   These figures were exactly
repeated in 10.27, subsequent to the onset of the anginous attacks.   The cardiac
sounds were never quite pure.   In 1921 the first sound at the apex was partially
replaced and succeeded by a soft short murmur.   In 1922 the murmur was
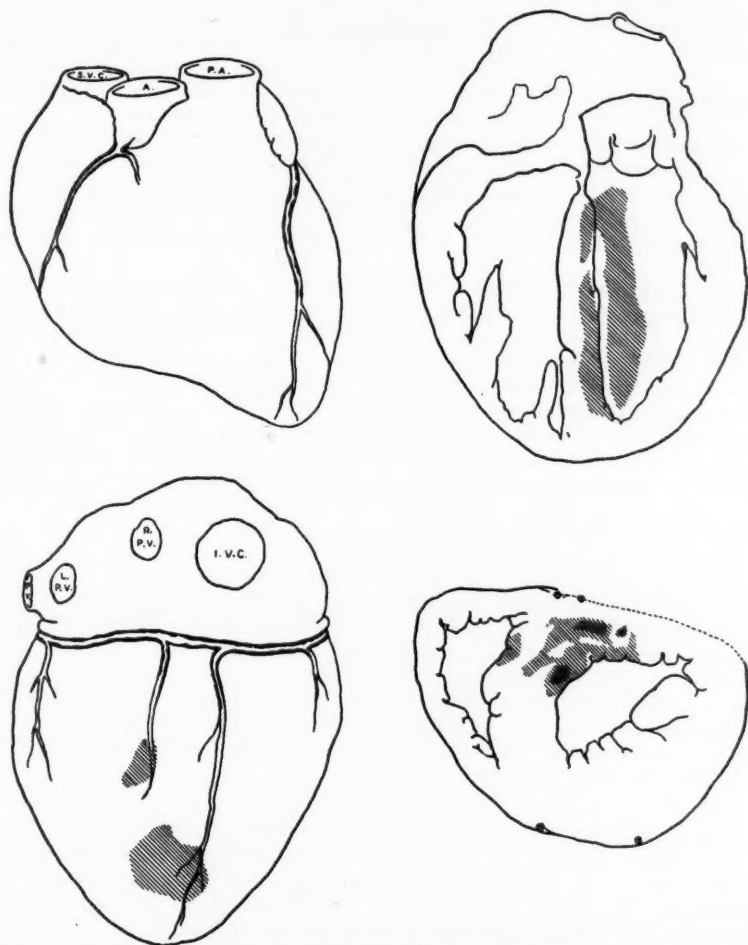
FIG. 2.   Case I.   Diagrams of the distribution of the fibrosis, and the arterial lesions.

shorter and less loud, in 1925 a little longer, and in 1927 definitely louder and
longer, wholly replacing the first sound.   In 1921 and 1922 the second pulmonic
sound had the emphasis, but subsequently the aortic second was the louder.
The blood-pressure did not vary greatly.   The systolic pressure was in 1921
165 mm. Hg.; in 1922 150 mm., 1925 130 mm., and in 1927 135 mm.   The
diastolic pressure varied between 85 and 95 mm.

The electrocardiograms showed but little change.   The P–R interval
measured 0·16–18″, QRS 0·10″, Q–T 0·38–42″, in the four electrocardiograms.
The QRS complex showed some change.   In 1921 lead III showed a well-
marked W, the central deflexion barely exceeding the base line.   Three months

later it was larger, rising above the base line. In 1925 a somewhat thick Q was followed by a small R, and in 1927 both deflexions were larger. T I and III were throughout opposed. In 1921 T III measured 0·75 cm., in 1925 0·45 cm., and in 1927 only 0·30 cm. R I was always larger than R III, and showed some general thickening, with a special thickening on the upstroke. (Fig. 1.)

The heart alone was examined *post mortem*. It weighed 17½ oz., both ventricles being dilated and hypertrophied. There was a considerable excess of subepicardial fat. Two ill-defined areas of fibrosis were present on the posterior aspect of the left ventricle; one, small and slightly depressed, adjacent to a descending branch of the coronary artery, about the middle of the ventricle; the other, which was much larger, around the terminal branches.

On section an extensive, rather patchy, area of fibrosis was found to be present, involving the posterior third of the interventricular septum over nearly its whole extent, and the adjoining half of the posterior ventricular wall from just below the attachment of the mitral valve down to the apex. The fibrosis reached the surface of the heart at the two areas which have been mentioned. (Fig. 2.)

The aortic cusps showed advanced sclerosis, with extensive calcareo is deposit, particularly in the right posterior cusp. This had produced a definite narrowing of the aortic orifice. The aorta above the valve showed marked atheroma with calcification, the divided wall being notably thickened. The orifice of the right coronary artery was narrowed to about half its normal calibre. Below this the first two inches of the vessel showed extreme narrowing from atheromatous change with concentric calcification. Lower down the artery was, in places, almost completely obstructed by atheromatous patches. The origin of the terminal descending branch was involved in a large atheromatous patch. The left coronary artery showed similar changes, especially in the smaller branches, the larger vessels being less affected.

The other cardiac valves were little altered.

There are several points of interest in the case. The patient had a large infarct of the heart in December 1920, and lived until February 1928, working hard for more than five of these years. Some six months before his death anginous attacks ensued *for the first time*; death eventually ensuing in an attack. A careful examination of the heart a couple of months after the anginous attacks commenced failed to reveal any change in the organ, though his blood-pressure was then definitely lower than it had been formerly. Post-mortem examination of the heart showed no recent changes in the muscle; merely the scar of the infarct of 1920.

Case II. The patient was a labourer, aged 50, at his death in 2.28.

The history is imperfect. It is known that he had been a heavy drinker for many years. He said that he had had growing pains in childhood, and scarlatina at 23. Four years prior to his admission he had an attack of 'rheumatic fever', which kept him off work for six months.

Some three years prior to admission into hospital, shortly after he had restarted work, he caught cold, the sputum at first yellow, becoming red later on. He became short of breath. These symptoms continued, and a year later he noticed that his feet were swollen. At this time he was confined to bed for about a month, after which he resumed his work, but he was soon forced to cease as his symptoms continued. In the autumn of 1927 he had a severe attack of bronchitis; and another, accompanied by a large haemoptysis, in January 1928. He was forced to take to bed. Oedema ensued and he was very restless and uncomfortable, with attacks of breathlessness from time to time, which came and went more or less abruptly, lasting for 5–10 minutes at a time.

On admission he was found to be large and stout, sitting bolt upright in
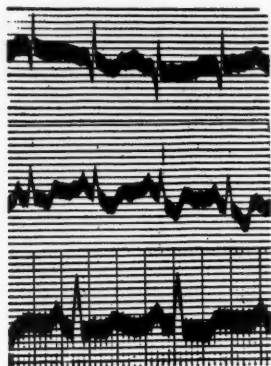
FIG. 3.   Case II.   7.2.28.
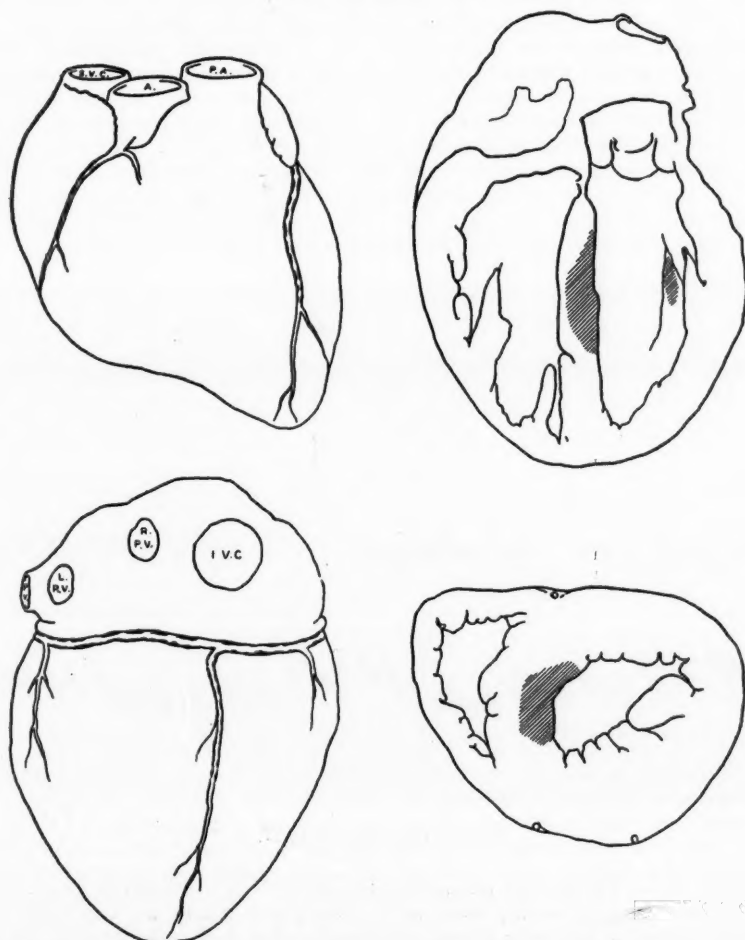
FIG. 4.   Case II.   Diagrams of the distribution of the fibrosis, and the arterial lesions.

bed, with an unhealthy, cyanotic, complexion, and oedema which extended up to the trunk. His breathing was frequent, and at times Cheyne-Stokes in character. The liver was much enlarged. The base of the right lung was dull to percussion, and there were rales at both bases. The urine showed a low S.G., and a trace of albumin.

Both sides of the heart were enlarged, the apex, in the seventh interspace, being 18 cm. from mid sternum. The cardiac sounds were distant and probably pure, but the respiratory noises interfered with accurate auscultation. The pulse was regular, about 80–90, with a high blood-pressure, 225–235 systolic, and 115–130 diastolic. The arteries were slightly thickened. His progress was unsatisfactory and he died suddenly a fortnight after his admission.

The electrocardiogram was not strikingly altered. R II and III showed some thickening and T II emerged directly from R without the normal isoelectric period. (Fig. 3.)

Post-mortem examination showed widespread and extreme senile atheroma of many vessels. In the aorta there were a few patches near the valve, with an extreme change beneath the diaphragm, most marked at the lowest part. The arteries of the spleen, liver, brain, and kidneys were grossly deformed. In the coronary arteries the degeneration was extreme and widespread. Many vessels were greatly narrowed and the branch of the anterior coronary artery to the septum was almost occluded. The anterior part of the septum showed a patchy but fairly abundant fibrosis, and the anterior papillary muscle was also involved. Both ventricles were enlarged and hypertrophied. The mitral valve was normal, the aortic cusps showing slight irregular thickening. The kidneys did not appear to be grossly abnormal, though the blood-pressure, as already mentioned, was high. (Fig. 4.) It is, of course, well known that disease of the splanchnic arteries is commonly associated with a high blood-pressure.
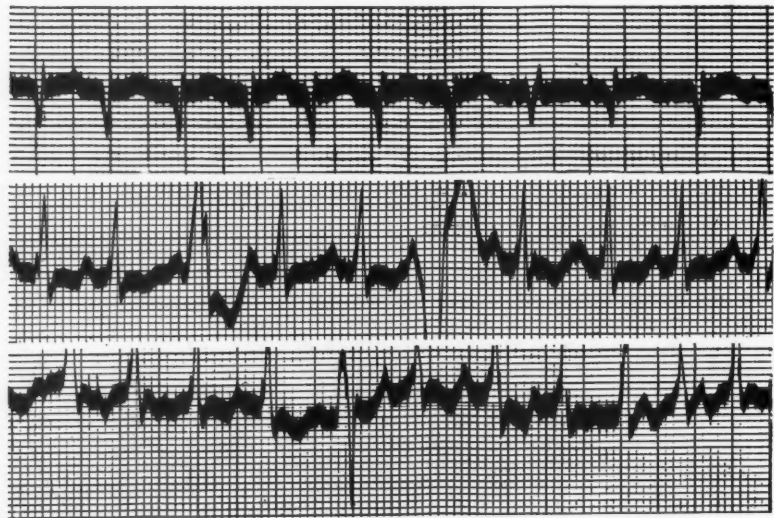
FIG. 5. Case III. 23.10.27.

Case III. The patient was a labourer, aged 66 at his death in 10.27.

He had been a healthy man until three years before his admission into hospital, when he had some illness which prevented him from working for six months. At that time his chief symptoms were headache and giddiness. When

he resumed work he found that he was less fit and short of breath upon exertion, but as his job was light he was able to carry on. A year later he began to experience pains in his chest, which seem to have been more or less constantly present and exaggerated by exertion. The pain was substernal in site. All his symptoms became gradually more severe, and he had to stop work in August, but, notwithstanding, all his discomforts tended to increase.
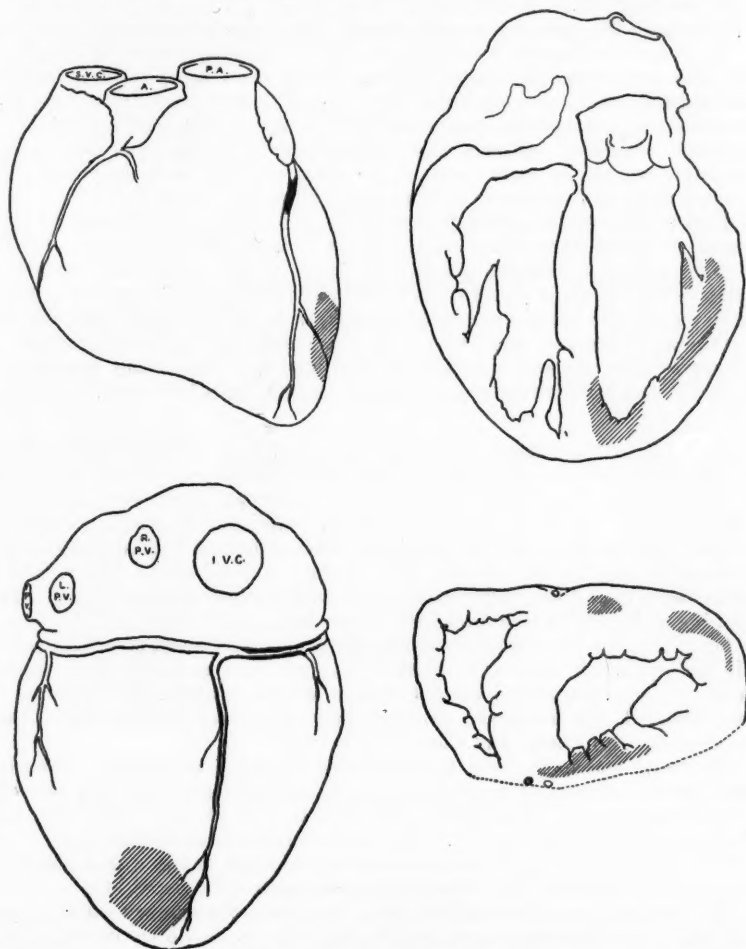
FIG. 6. Case III. Diagrams of the distribution of the fibrosis and the arterial lesions.

On admission he was found to be a slimly-built man of poor nutrition, very frail, breathless, and slightly cyanosed. At times he had attacks of breathlessness, and he sometimes complained of headaches. There was no oedema or enlargement of the liver, but râles were present at the bases of the lungs. Both sides of the heart were greatly enlarged, the apex being in the sixth interspace, 13·5 cm. from mid sternum. The cardiac sounds were distant and short, the first sound at the apex being followed by a short blowing murmur. The second sounds were sometimes reduplicated, and the aortic element was accentuated and intoned. The radial artery was thick and hard and the blood-pressure was

high, 210–140 mm. Hg.   The pulse was frequent, running about 95, and irregular from occasional extra-systoles.

He tended to ‘wander’ at night, and his breathing was sometimes Cheyne-Stokes in character.   The congestion at the bases of the lungs increased, oedema appeared in the feet on 18.10, and steadily increased in amount, and after 21.10 he became incontinent.   He was now slightly feverish, and his pulse failed and he died on 24.10.27.

Clinically the case was a senile heart, with anginous and toxic symptoms.

An electrocardiogram was taken on 23.10.27, the day before his death.   The pulse was now frequent and irregular.   There were many ventricular extra-systoles, both right- and left-sided, and, in addition, an indefinite irregularity, the ventricular contractions sometimes succeeding an apparently normal P, and sometimes occurring without any evidence of auricular activity.   All the ventricular complexes, save those of the extra-systoles, were, however, similar, and apparently in response to a supra-nodal stimulus.   (Fig. 5.)

Post-mortem examination showed cirrhotic kidneys, and widespread arterial disease.   Infarcts were present in the lungs, kidneys, and the heart.   The latter was much enlarged, both sides being affected.   There was a patch of old peri-carditis on the anterior aspect of the left ventricle, about 2″ from the apex, the underlying muscle being exceedingly tough, from an advanced fibrosis.   Some old-standing thrombus was present on the corresponding endocardium.   The coronary arteries showed extensive disease, and the descending branch of the left artery was completely occluded about an inch from its origin.   (Fig. 6.)

Case IV.   The patient was a painter, aged 51.   He had been a healthy man, and had not had any illnesses of any importance prior to his last illness.

At Christmas time, 1927, he contracted ‘influenza’ and was confined to bed for three weeks.   When he got out of bed he found that he was somewhat short of breath upon exertion and felt his heart beating, but he continued at his work. Two months later he caught cold, and bronchitis developed.   His ankles now became swollen, and the palpitation and breathlessness became worse.   In the beginning of March he was forced to take to bed.

On admission into hospital on 18.4.28 he was very short of breath, and had to sit bolt upright in bed.   The extremities were cyanosed, and there was some oedema.   Cough was troublesome, but there was no sputum.   The cervical veins were distended, the liver was enlarged, and there was dullness for a hand’s-breadth at the right base, and râles at both bases.

The heart was large, both borders being displaced outwards.   The cardiac sounds were short and of poor quality, and a systolic murmur was audible at the pulmonary area.   The pulse was regular and of fair value, the blood-pressure being 150–110 mm. Hg.   The urine contained some albumin.

The left fundus showed several spots of yellowish exudate, and some retin-itis about the macula.   The vessels seemed in quite good condition.

His progress was never satisfactory.   At times the urinary output became ample and the oedema decreased, and he was able to lie down in bed ; but on the whole any improvement was of short duration and succeeded by an exaggera-tion of his previous discomforts.   The oedema increased and frequently required tapping.   In May his sputum for a time contained some blood.   In August pleural friction appeared on the left side.   Towards the end of September the oedema became greater than before and the râles at the bases more copious.   On 17.10 his temperature, which throughout his residence had only exceeded normal on two or three isolated occasions, rose to 101°, and his sputum, which for long had been mucopurulent, again became blood-stained.   A definite consolidation was now apparent at the right base.   He had been steadily losing flesh and strength, and his face was now thin and blue.   He died somewhat suddenly on 19.10.28.

His pulse-rate throughout his residence was always frequent, running about 90–100, unless when slowed by heavy dosing with the digitalis group of drugs, or from the occurrence of extra-systoles. His blood-pressure remained unchanged until August, when it commenced to fall, reaching 110–80 in September. Subsequent records were impossible to obtain. His urine never contained albumin in amount, and was generally free from it, though in April, May, and September it showed appreciable amounts. The clinical picture was throughout one of a progressive cardiac failure. There was no evidence of toxaemia until a few days prior to his death.

Electrocardiograms were taken on 20.4, 23.6, and 11.10.28. The only suggestions of myocardial lesions are the thickening of R and the flatness of the T's. The second electrocardiogram showed many extra-systoles, of ventricular origin, all but one being left-sided. (Fig. 7.)

20.4.28.   23.6.28.   11.10.28.
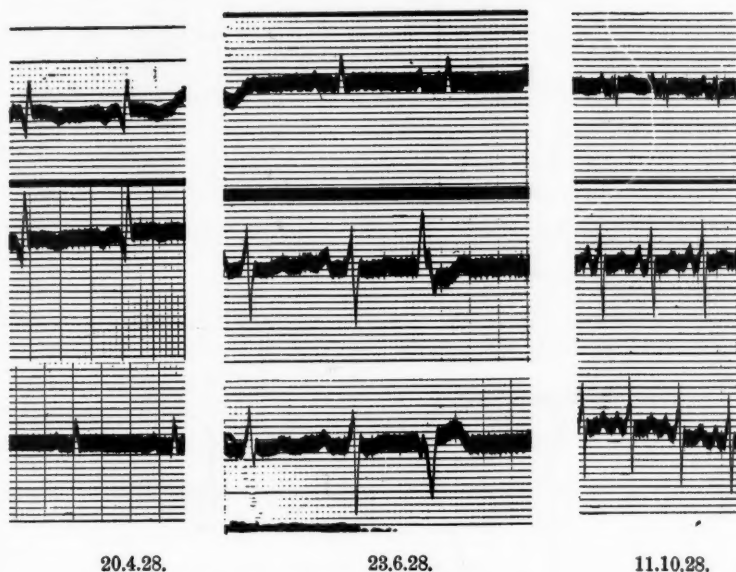
Fig. 7.   Case IV.   Electrocardiograms.

Post-mortem examination showed some arteriosclerosis and atheroma of the aorta. The kidneys showed some arteriosclerotic changes. Recent pneumonic consolidations of both lungs were present. The spleen was enlarged and hard.

The aortic cusps were slightly thickened. The other valves were normal. The coronary arteries were the seat of extensive atheromatous changes, a dense patch almost occluding the lumen of the descending branch of the left coronary artery, about two inches below its origin, while the right artery was greatly narrowed about an inch and a half from its orifice; and, again, immediately before the origin of the main descending branch.

The pericardium was normal, but a small area of the anterior wall of the left ventricle just above the apex appeared to be puckered, and there was a larger area about an inch and a quarter higher up, in the line of the left descending branch, which appeared to be thinned. On section of these areas the wall of the ventricle was found to be thinned and dense, the muscle being

practically replaced by fibrous tissue. The endothelium lining these areas was greatly thickened, and greyish-white in appearance. (Fig. 8.)

The appearance suggested a dystrophic fibrosis rather than an infarct.
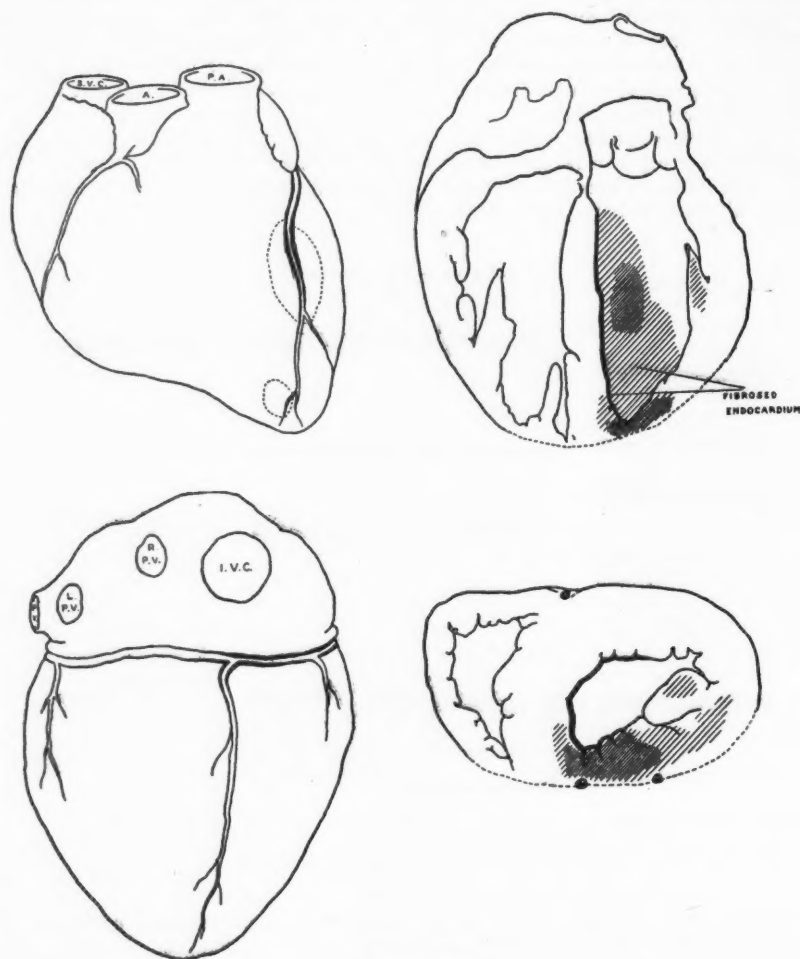
FIG. 8.   Case IV.

Summary.

The foregoing paper is a corollary of that on the ventricular complexes in myocardial infarction and fibrosis, which appears on page 273 of this Journal. Four cases of coronary artery disease are described with a history of cardiac ailment up to eight years.   In the first case, after the initial coronary occlusion with the usual symptoms, working capacity was maintained for seven years.   Then followed anginal attacks for six months, in one of which death

occurred.   No recent cardiac disease was found, but there was an old scar in the field of the right coronary artery.   In the second case there was a three years' history of cardiac enfeeblement, with hypertrophy and dilatation, ending in congestive failure and sudden death.   The arterior coronary artery was almost occluded, and there was fibrosis in the muscle supplied.   In the third case, again with three years' history, an enfeebling illness was followed, after six months, by anginal attacks.   Towards the end of his illness there occurred attacks of breathlessness and slight mental change.   Oedema of the feet was present a few days before death.   The descending branch of the coronary artery was occluded and there were patches of fibrosis in the ventricular wall.   In the fourth case there was a history of gradual congestive failure and the heart showed that the descending branch of the left coronary was almost occluded and the right coronary was markedly narrowed.   There was dystrophic fibrosis in the left ventricular wall and part of the septum.

Case I presented the T III type of inversion after infarction of the posterior ventricular wall, thus conforming with the opinion held by Barnes.   The inversion, first observed 37 days after the infarction, had not disappeared $6\frac{1}{2}$ years later.   In the remaining cases extensive fibrosis of the ventricular muscle and chronic occlusion, partial or complete, of main coronary arterial branches were not associated with characteristic electro-cardiographic changes. In the light of our present knowledge the abnormalities that were recorded cannot be regarded as definite localizing signs.   The variation in the form of the ventricular complexes in Case IV indicates the need for further study of serial records in cases of myocardial fibrosis.
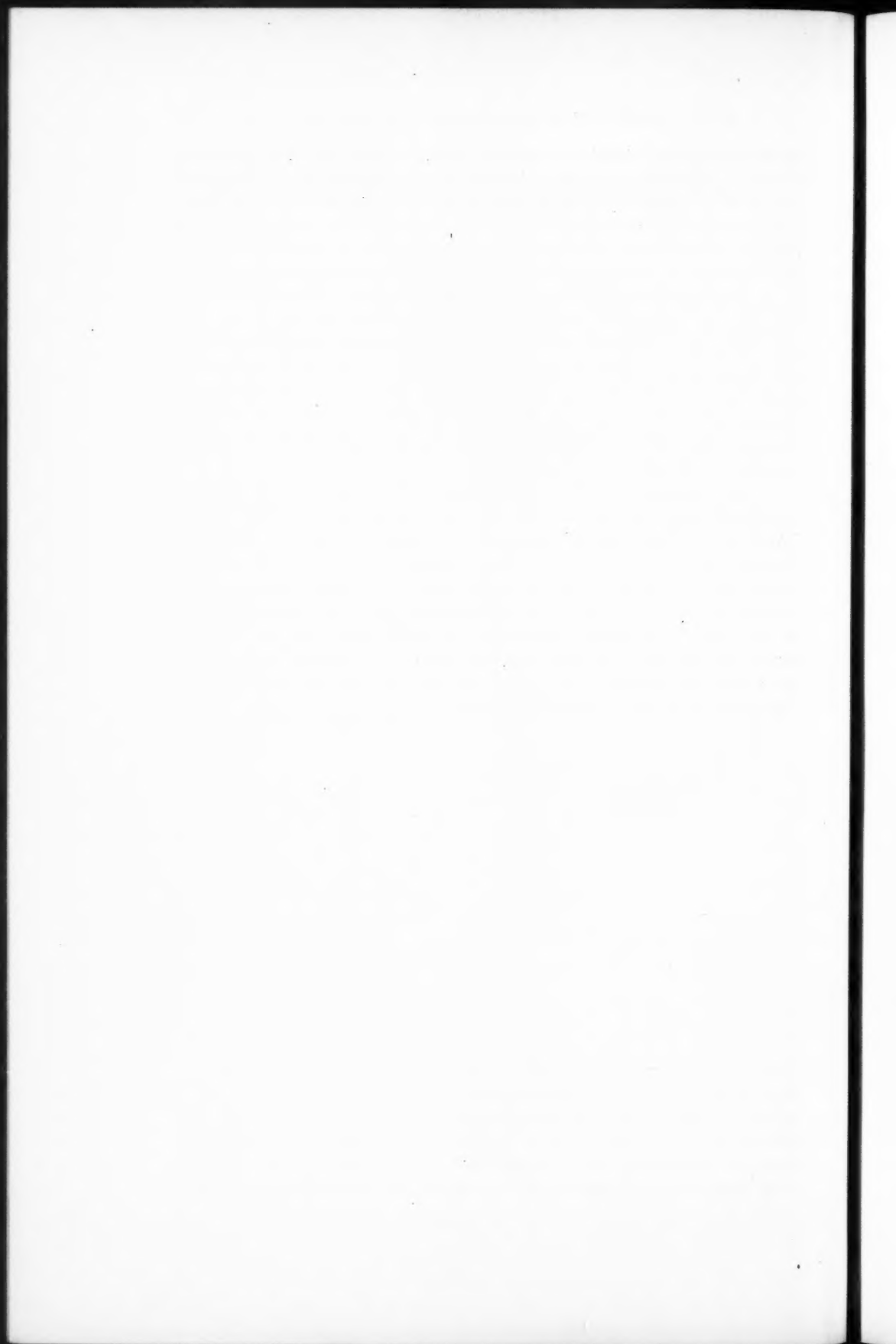
A CASE OF PARADOXICAL EMBOLISM WITH BLOOD-CLOT LODGED IN FORAMEN OVALE [1]

By WILLIAM G. BARNARD

(From University College Hospital Medical School, London)

With Plate 16

SPECIMENS in which masses of blood-clot are actually trapped on their way through a patent foramen ovale and thus demonstrate the possibility of a paradoxical embolus are rare. Thomson and Evans, in their recent review of cases, mention only seven altogether, six in which thrombus and one in which a mass of growth was caught in this way. The additional case here described is of interest in respect of their arguments regarding the manner in which the relative pressures in the left and right auricles are disturbed so that a current of blood may commence to stream from right to left auricle and carry clot with it through an opened foramen.

Description of Case.

The patient, a well-nourished and well-developed man of 63, was under treatment for a carcinoma of the prostate. A suprapubic cystostomy was performed and radium inserted into the growth. Recovery was satisfactory, and the patient was getting up at the end of a fortnight. On the 16th day he was kept in bed on account of symptoms ascribed to indigestion ; in the evening of that day he died quite suddenly while talking to another patient.

At the post-mortem examination a mass of coiled, mixed red, pink, and grey laminated clot with a rippled surface was found completely filling the right and left pulmonary arteries and extending for a short distance into their main branches. An entirely separate clot of similar formation and about 15 cm. long was caught in the foramen ovale in such a way that its greater length hung free in the left auricle and down into the left ventricle, while a much shorter, thicker part projected into the right auricle. This clot was covered by a thin pink pellicle, which was finely mottled and stippled with white, giving it the typical rippled surface of ante-mortem clot. The pellicle was unbroken, so that the clot appeared complete in itself and had not the appearance of being broken off from a larger clot. The part projecting into the right auricle presented two deep grooves, which would correspond perfectly to the markings of semilunar valves in a vein of the size of the femoral just above its junction with the internal saphenous vein. At the level of the mitral valve the long arm of the clot on the left side was much thinner and twisted as if it had been nipped by the closure of the valve and the distal part had been twirled in the blood-stream, and this appears to be the most reasonable explanation for its peculiar appearance.

The foramen ovale was guarded by a valve which was attached to the circumference of the annulus ovalis except at its upper anterior margin, and the clot had passed forward as well as to the left to get through this deficiency. With the clot *in situ* the opening measured 0·7 cm. in diameter; the clot immediately to the right was 1·2 cm. in diameter, and although the portion which had been carried through to the left side measured in its thickest part 1 cm. diameter, it is probable that the remainder did not get right through because it was just too thick to do so. At the point where it had passed through the interauricular septum the clot lay between the anterior pillar of the foramen ovale anteriorly and the valve posteriorly.

There was fluid blood elsewhere in the left ventricle and there were no clots in the aorta. The valves of the heart were natural. A single small (1·5 × 1·5 × 0·5 cm.) pale patch was noted in the upper pole of the spleen and thought to be a recent infarct; no other infarct was seen naked eye. On microscopic examination this proved to be a patch of recent necrosis infiltrated round its borders by polymorphs, and was without doubt a recent infarct. Although it had not been identified with the naked eye, a microscopic section of the kidney revealed a small recent infarct in the cortex. This was triangular in outline with its base towards the capsule and its apex just reaching the medulla; the cells lining the tubules were dead, but many of them still contained pyknotic nuclei or remains of nuclei, and the capillaries in its periphery were engorged. No clot was found in the vessels in the neighbourhood of these infarcts. There were no infarcts in the lungs. Fluid blood was found in the inferior vena cava, iliac, and uppermost part of the femoral veins. It was impossible to examine the veins of the extremities because permission could only be obtained for an incision limited to the trunk.

The prostate had been largely replaced by growth which had infiltrated the urethra and the interior wall of the rectum, and the only secondary carcinoma found was a single nodule in the right iliac lymphatic gland. On microscopic examination the growth proved to be a tubular, cubical, and columnar-celled carcinoma.

Commentary.

Beattie analysed the way in which a large embolic or thrombotic obstruction of the outlet by the pulmonary artery must raise the pressure in the right ventricle and auricle, while the pressure on the left side will fall at the same time on account of the diminished intake of blood from the lungs; and he pointed out that these changes will cause blood to pass from right to left through a foramen ovale that might otherwise have remained closed by the valve covering it on the side of the left auricle. Thomson and Evans accepted this view in explanation of the cases which they described. In the present case it is probable that minute emboli got through the patent foramen ovale some hours before death and were the cause of the recent infarcts in the spleen and kidney, which may have been responsible for the symptoms loosely ascribed to indigestion on the last day of life. No secondary carcinoma was found in sections of either organ, nor was there a general dissemination of cancer, so that it seems reasonable to assume that the infarcts were secondary to emboli which were derived from thrombus which must have been present in some of the large veins. In Beattie's first case, which resembled this in having an infarct in the kidney, there was some evidence that one pulmonary artery was blocked about two

hours before the other, but there was no evidence of a similar sequence of events in this case. Apart from the minute emboli, the probable sequence here was that large clots from femoral or iliac veins were carried to the right side of the heart and passed on to the main pulmonary arteries which they blocked. As a result, the right side of the heart dilated and the normal intra-auricular pressures were reversed, so that the foramen ovale gaped and blood flowed freely through it: consequently the next clot to arrive was carried through the foramen until it stuck in the opening and closed this flow of blood from the right to the left side of the heart. After this there were almost certainly a few more heart-beats, as shown by the twisting of the clot in the left ventricle, and then the heart stopped.

Apart from the suggestion that the valve of the foramen ovale was not sufficiently competent to prevent the early passage of minute emboli, this example is in harmony with the explanation of these cases given by Beattie and quoted above. But the clinical history of practically sudden death is a difficulty which can only be avoided by supposing that the blockage of the pulmonary artery was almost immediately followed by the passage of a separate clot through the foramen ovale as the heart was making its last beats.

REFERENCES.

Beattie, W. W., *Internat. Am. Mus. Bull.*, N. York, 1925, xi. 64.
Thomson and Evans, *Quart. Journ. Med.*, Oxford, 1930, xxiii. 135.

DESCRIPTION OF PLATE.

Heart with formed ante-mortem clot caught in foramen ovale. The letter A marks the twisted portion of pellicle sheath, with very little thrombus inside it, where the clot lay at the level of the mitral valve. Beyond this the clot is of full diameter again as it reaches down the left ventricle.

A

THE AETIOLOGY AND PROGNOSIS OF AURICULAR FIBRILLATION [1]

By HAROLD COOKSON

(From the Cardiographic Department of the London Hospital)

THERE are certain obvious consequences of fibrillation of the auricle, such as the lowered efficiency of the ventricle, which must result from its irregular contraction, especially when it is also rapid (24), (34), (45). Another is the absence of effective auricular contractions, though this in the experimental animal was found by Lewis (24) to play a negligible part in the production of circulatory changes. Yet there are other factors, not self-evident, which come into operation only with the advent of the arrhythmia. It is the main object of this paper to present some clinical evidence as to the bearing of these factors on prognosis.

The Aetiological Varieties of Auricular Fibrillation.

Although auricular fibrillation has been attributed to a great variety of causes, there are only three common aetiological groups in which the disorder is persistent. In the commonest it is associated with rheumatic heart disease; in the second most common group there appear to be no constant associated conditions, except that of age; and in the third there is exophthalmic goitre or some allied toxic thyroid state. The second group, containing patients who have reached middle or old age, has received several names, none of which is entirely satisfactory. Thus it has been termed the 'arteriosclerotic' type; it is true that some thickening of the peripheral vessels will usually be found in these patients, but it is no more than is expected at the age-period concerned; and conversely in those with conspicuous hardening of the arteries, normal rhythm is the rule. Also, in coronary thrombosis, which nearly always occurs in atheromatous vessels, fibrillation is not commonly found; it occurred in paroxysmal form in 7 per cent in a series of one hundred cases (39). The histological evidence, what little there is of it, fails to incriminate the blood-vessels. Yater (54), in a microscopic study of a large number of auricles from cases of auricular fibrillation, examined six specimens from hypertension cases and two from cases of coronary sclerosis. These showed only slight changes in the auricular arterioles.

The records of the London Hospital Pathological Institute furnish details of the post-mortem findings on ten cases of the so-called arteriosclerotic type.

[1] Received February 19, 1930.

TABLE I.

Post-mortem Findings in Ten Cases of Non-rheumatic Auricular Fibrillation.

Case No.	Sex and Age at Death.	Degree of Atheroma of Coronaries.	Degree of Atheroma of other Arteries.	Condition of Kidneys.	Other Conditions.	Heart Weight.
1	M. 59	Few flecks	Numerous buttons and flecks in large arteries	Congested. Slight focal distortion of cortical pattern	Carcinoma of caecum. Thrombosis of inferior vena cava. Pulmonary Embolism	18¼ oz.
2	M. 61	Partly calcareous buttons	Considerable (numerous buttons)	Granular	Cirrhosis of liver	19¾ oz.
3	M. 55	Numerous buttons	Severe in aorta. Considerable in other large arteries	Secondary ischaemic nephritis	Nil	22½ oz.
4	M. 55	Confluent flat flecks	Numerous buttons and flecks	Tuberculosis	Tuberculosis of pericardium and bladder	19½ oz.
5	F. 63	Numerous flecks and a few small buttons	Numerous flecks and small calcareous buttons	Slightly granular	Nil	20 oz.
6	M. 39	Few flat flecks	Considerable (ridges and buttons)	Chronic nephritis	Cirrhosis of liver. Bronchopneumonia	22¾ oz.
7	M. 60	Thick plaques of atheroma in left coronary	Aorta thick-walled. Few flecks at commissure	Slightly granular	Nil	Heart considerably enlarged
8	F. 71	Few flecks	Severe.	Oedema only	Purulent cholangitis	10½ oz.
9	M. 52	Considerable thrombosis of left anterior descending	Very severe	Infarction of r. kidney secondary to thrombosis of renal artery	History of high blood-pressure	26 oz.
10	M. 60	Few flecks	Few flecks and atrophic buttons	Severe parenchymatous degeneration	Lobar pneumonia and abscess	12 oz.

Rheumatic heart disease was excluded, as far as possible, by a negative history and the absence of valvular lesions. They were also free of any syphilitic lesion (macroscopic), and hyperthyroidism was excluded by the history and by a post-mortem examination of the thyroid gland. The average age at death was fifty-eight; eight of the patients were men, only two women. The findings at autopsy are set out in Table I. Examination of the coronary arteries showed that the lumina were not narrowed, except in one case in which there was a thrombus in the anterior descending branch of the left coronary artery, and a recent infarct of the interventricular septum. In this case alone was there

TABLE II.

Post-mortem Findings in Ten Control Cases of Heart Disease with Normal Rhythm.

Case No.	Sex and Age at Death.	Degree of Atheroma of Coronaries.	Degree of Atheroma of other Arteries	Condition of Kidneys	Other Conditions	Heart Weight.
1	M. 68	Severe. Numerous buttons and flecks	Very severe ; numerous buttons, plaques, and ulcers	Chronic nephritis	Broncho-pneumonia	18¾ oz.
2	M. 39	Moderate ; fat flecks and small buttons	Moderate ; flecks, small buttons, and a few large plaques	Ischaemic nephritis	—	24¼ oz.
3	F. 52	Few flecks	Flecks and a few small buttons	Firm ; slightly congested	Acute on chronic bronchitis ; emphysema	11½ oz.
4	M. 40	Few small buttons	Moderate	Sub-acute toxic on chronic ischaemic nephritis	Infarction of lungs	18¾ oz.
5	F. 56	Thick buttons causing slight stenosis	Confluent fatty and fibrous plaques, areas of calcification	Chronic nephritis	Fibrinous pericarditis; areas of haemorrhage in wall of left ventricle	16½ oz.
6	M. 48	Fatty buttons	Considerable ; fatty and fibrous buttons	Chronic nephritis	Broncho-pneumonia	21 oz.
7	M 62	Confluent fatty buttons	Severe	Chronic nephritis	Broncho-pneumonia. Area of fibrosis in interventricular septum	23 oz.
8	M. 62	Severe; confluent fatty buttons with calcified areas; considerable stenosis	Considerable	Congested	—	22¼ oz.
9	M. 62	A few small buttons	Severe ; numerous buttons, plaques, and ulcers	Chronic nephritis	Cerebral haemorrhage	16¾ oz.
10	M. 62	Severe ; confluent buttons with calcification causing stenosis	Severe ; confluent calcareous buttons, and some ulcers	Congested	Diabetes	16½ oz.

considerable atheroma of the coronaries; in the other nine it was slight, amounting usually to not more than 'numerous fat flecks' or 'buttons'. There was, however, considerable atheroma of the other arteries in some of the cases, and also ischaemic changes in the kidneys. In this series, therefore, there is no justification for the use of the term 'arteriosclerotic' to be obtained from the coronary arteries. Ten controls have been examined, and the post-mortem results are seen in Table II. These cases had normal rhythm, otherwise they are comparable with those in Table I—that is, in so far as the age, sex, and freedom from rheumatic, syphilitic, and thyroid disease are concerned. If the atheromatous lesions of the coronaries in the two series are compared, it will be seen that they are more extensive in those with normal rhythm (leading to stenosis of the artery in three cases) than in those with fibrillation. There is therefore definite evidence for rejecting the term 'arteriosclerotic auricular fibrillation'.

High blood-pressure occurs in a proportion of the cases, but not with sufficient frequency to entitle it to be regarded as an important aetiological factor. Raised blood-pressure usually leads to failure with normal rhythm (38). Again, it is not common to find a high pressure in those patients in whom normal rhythm has been restored with quinidine (40). Hypertension was present in 12 out of 70 cases investigated by Wolff and White (53), and Campbell (5), found a pressure of 170 or more in twelve out of a hundred cases.

The 'senile type' is another term which has been applied to the group under consideration, but it must be rejected as it exaggerates the average age incidence. In French literature it has been called the 'primitive type' because it seems to arise from no known cause. From the numerical point of view this type is second only to the rheumatic as a cause of persistent auricular fibrillation, and it is suggested that it may be conveniently referred to as the non-rheumatic group, from which, of course, the distinct and smaller group of toxic goitre cases is excluded. This term, at least, does not disguise the fact that the cause is as yet unknown.

In four years 361 cases of fibrillation were admitted to the London Hospital; 249 (69 per cent.) had rheumatic heart disease or gave a history of rheumatic fever; 79 (22 per cent.) were of the non-rheumatic type; 26 (7 per cent.) occurred with exophthalmic goitre, and 7 (2 per cent.) with syphilitic aortitis.

The Relation of Aetiology to Prognosis.

A comparison of the prognosis in the two chief groups, the rheumatic and the non-rheumatic, has been made by several authors; it is usually considered to be better in the rheumatic (7), (10), (21). On the other hand, Clerc and Stieffel (6) considered that the non-rheumatic group had the better outlook.

To determine the expectation of life in these two groups, a series of cases where the date of onset of the arrhythmia was almost exactly known has been

followed up, either till death or for a minimum period of five years. In the rheumatic group, cases of 18 years of age or more are considered; those of 17 or under will be dealt with separately. There were 55 cases of this type; 47 have died, 7 are still alive, and 1 could not be traced; the average duration of life after the onset of the arrhythmia was 5¼ years. In a smaller group of non-rheumatic cases, comprising 13 patients, 9 have died, and 4 are still alive; the average duration was 7 years, a period which definitely exceeds that found for the rheumatic group, and which opposes the consensus of opinion that the outlook is better in the rheumatic cases.

The association of failure and fibrillation is one familiar to all clinicians, but it was considered that the precise relation of the two conditions in point of time was worth examination in the two chief aetiological groups. In 32 rheumatic cases, failure coincided with the inception of fibrillation in 13, preceded it in 8, and followed it in 11. In 12 cases of the non-rheumatic type, failure occurred with the onset in 8, preceded it by a year in 1, and had not appeared during the period of observation in 3. The figures show, contrary to what might have been expected, a higher proportion of cases developing failure at the onset of fibrillation in the non-rheumatic than in the rheumatic group. A similar finding is reported by Campbell (5); he notes a sudden appearance of symptoms with the onset of fibrillation nearly as often in the 'arterio-sclerotic' group as in the rheumatic.

<div align="center">TABLE III.</div>

The Expectation of Life in Rheumatic Cases with Fibrillation Classified according to Age of Onset.

Age at Onset of Fibrillation.	No. of Cases.	Duration of Life.
12–17	23	10 months
18–28	22	4·5 years
28–38	16	6·5 ,,
38–48	8	5·8 ,,
Over 48	9	4·1 ,,

<div align="center">Average duration in adults 5·25 years.</div>

The Relation between Age and Prognosis in the Rheumatic Group.

Examples of auricular fibrillation are hardly ever seen in the first decade, and are still more rare in the second. In a series of 35 cases collected from hospital records (9), aged 12–17, and representing an incidence of about 2·5 per cent. of all cases of the disorder, the sex ratio was 3 girls to 2 boys—a smaller numerical superiority of the female than in the adults, where the ratio was found to be 2 women to 1 man. The average duration of life with the arrhythmia in 23 cases of this series which have died of heart disease was 10 months. In 19 of these it was 9 months or less, that in the other 4 being relatively long, with a maximum of 5 years and 2 months. The shortest duration was 3 weeks. Treatment was found to afford little or no relief in these young individuals, and

once the arrhythmia is installed the patient is usually confined to bed with gross failure till death.

A further analysis of the rheumatic cases shows that after the second decade the age of onset of fibrillation has little effect on the prognosis. In the decade following adolescence the period was 4·1 years, with a slightly shorter one for those over 48, but definitely longer in the intervening years (see Table III).

The Relative Incidence of Embolism in Mitral Stenosis with and without Auricular Fibrillation.

Embolism, an important complication of mitral stenosis, has received a good deal of consideration since the introduction of quinidine into the therapeutics of auricular fibrillation. In the earlier period of the use of this drug, fears were aroused that the restoration of normal rhythm might be an advantage discounted by the occurrence of embolism. Later reports are, however, more sanguine, and Viko, Marvin, and White (47), dealing with large numbers of patients, found embolism less common in quinidine-treated cases than in controls, and Parkinson and Campbell (40), from their own and other cases abstracted from the literature, reach a similar conclusion. Lewis (25) stated that pulmonary embolism occurred with no greater frequency in fibrillation than in sinus rhythm; an estimate based on the number occurring in the lungs is, however, open to the objection that there is often difficulty in diagnosing the lesion in this site.

To form some opinion as to the frequency of embolism in mitral stenosis with fibrillation, as compared with the frequency while the rhythm remains normal, the London Hospital records for the period 1914–28 were examined for all cases admitted with mitral stenosis and hemiplegia, the last indicating a cerebral embolus. Of the situations where embolism is possible, the brain may be regarded as the most serious, and also as the site where its occurrence is least likely to be overlooked, or confused with other lesions. Further, the numbers of cases admitted to the wards will be fair samples of the incidence of the condition, since all cases brought up with mitral stenosis and cerebral embolism are likely to be admitted whether fibrillating or not. A total of 69 cases of mitral stenosis with cerebral embolism was found, in 35 of which normal rhythm was preserved and in 34 the auricles were in fibrillation. It must therefore be concluded that embolus is about as frequent with normal rhythm as with the arrhythmia.

Auricular Fibrillation and Heart-block.

(1) *Partial block.* A minor degree of heart-block is represented by those cases in which the ventricular action is persistently slow, apart from digitalis administration, though quite irregular. In a group of ten such patients, whose ventricles were beating at about 70 at rest, but who showed no evidence of

complete heart-block, the prognosis was found to be rather better than where digitalis was necessary to control the ventricular rate. In these 10 cases, which were followed from the inception of the arrhythmia till death or for a minimum of 5 years, the average duration of life was $7\frac{1}{2}$ years. As 7 of the patients were in the rheumatic group, in which the average expectation of life of all adult cases was found to be $5\frac{1}{4}$ years, and only 3 belonged to the non-rheumatic group, this figure indicates an increased expectation of life. They also have an advantage in that they do not need to take any drug regularly. Even patients who are benefited by digitalis are often careless about regular dosage and suffer a series of breakdowns corresponding to acceleration of the ventricle when the supply of medicine is exhausted. Of a total of 17 cases of the type in which the ventricle was slow without digitalis, 11 were rheumatic and 6 non-rheumatic. This proportion of the non-rheumatic type is higher than occurs in the aetiological analysis given above of 361 cases, in which the ratio of rheumatic to non-rheumatic cases is about 3 to 1. A ventricle slow without treatment is not necessarily always so ; and reversely there are cases which resist digitalis therapy for a time, and yet subsequently require no treatment to control the ventricular rate. A girl of 17 showed this resistance to digitalis at the onset of auricular fibrillation. After 2 or 3 years' treatment the ventricle remained slow for 9 months without digitalis. Another, a woman of 36, with mitral stenosis, had a heart-rate of 70–80 for 6 years. After this time 20–30 minims of digitalis tincture daily was required to keep it within these limits. At this time failure made its first appearance, and her health has been less satisfactory during the subsequent 7 years.

The state of the conducting bundle, which prevents it from transmitting more than about 70 impulses per minute when the auricle is fibrillating, does not prevent it from conducting more than this number when it receives impulses from a normally contracting auricle, and a defect may then be revealed by a prolonged P–R interval in the electrocardiogram. Examples of this are recorded by Mackenzie (30) and Emanuel (14). Two cases in this series illustrate this phenomenon; one, with paroxysmal fibrillation, had a P–R interval of just over 0·2 second with normal rhythm and a ventricular rate never exceeding 90 with fibrillation, though untreated. In another, with coronary thrombosis, digitalis (in doses equivalent to 20 minims of the tincture per day) was given for two weeks, at the end of which time a paroxysm of fibrillation occurred, the ventricular rate falling at the same time from 110 to 60.

(2) *Complete block.* These two disorders of the heart-beat are seldom found in combination, apart from those cases of fibrillation to which heavy doses of digitalis have been given. This last type of complete block is usually transient, acceleration of the ventricular rate occurring when the drug is withheld ; but exceptions are described (35) (46). Sometimes the ventricular rate is relatively high in auriculo-ventricular dissociation due to digitalis (22) (23) (27). In uncomplicated dissociation auricular fibrillation has supervened after this drug has been given (35) (42). Apart from digitalis the two disorders of rhythm may

complicate rheumatic (1) (15) (29) 'arteriosclerotic' (1) (44), syphilitic (8), and diphtheritic (37) heart disease. The history suggests that coronary thrombosis was the immediate cause of both arrhythmias in one of the examples given by Mackenzie (29). In another, described by the last author, Adams-Stokes attacks occurred, and such attacks were the sequel to the onset of complete block in a case of auricular fibrillation to which large doses of digitalis and quinidine had been given (13). Otherwise there is no mention in the literature of fits occurring in association with the combination of rhythms. In comparison with the frequence of the attacks in block associated with normal auricular rhythm (49) (51), this certainly represents a low incidence. On the other hand, restoration of sinus control in two cases of complete block and fibrillation (2) was followed by a recurrence of fits. Similarly Gallavardin (16) records several instances of fibrillation and partial block, with syncopal attacks.

Five new cases of the combination have been studied—4 men and 1 woman, the average age being 62. High blood-pressure was present in four ; one of them had aortic incompetence (rheumatic) and one a history of syphilis in addition. Four had defective bundle-branch conduction. Two have died, death occurring three months and two years respectively after the date when fibrillation was first recognized. In the remaining three, who are all able to get about, the average duration to date with both disorders is 3½ years. Not one has suffered from Adams-Stokes attacks since the two arrhythmias have been present. It appears that fibrillation of the auricle does not add to the gravity of a case in which complete block already exists ; and it is possible that with its inception the liability to Adams-Stokes attacks may be less.

Cases with Auricular Fibrillation and Complete Block.

(1) Male, now aged 60. History of weakness, shortness of breath and swelling of the ankles coming on suddenly in 1926. No history of syphilis or rheumatic fever. Heart enlarged ; rate 42–86; signs of aortic stenosis and incompetence ; B.P. 340/150, falling with rest to 160/70. Arteries thickened ; electrocardiogram : auricular fibrillation and complete block ; ventricular complex low voltage, but otherwise normal. Congestive failure. W.R. negative. Orthodiagram : slight prominence of the pulmonary artery ; left auricle not enlarged in the oblique position ; enlargement to the left.

In 1928, gangrene of the right toe occurred ; the leg was amputated through the thigh, and the patient survived. In 1929, the patient was fairly comfortable and free from congestive failure.

(2) Female, now aged 66. History given in 1926 of giddiness for 'several years'; recent fainting attacks and convulsions. No history of rheumatic fever. W.R. negative. Heart moderately enlarged ; B.P. 220 (systolic). No failure. A few Adams-Stokes attacks occurred between July and September 1926. Electrocardiogram (November) showed auricular fibrillation, complete block, and a right bundle-branch lesion.

A later electrocardiogram showed variable conduction down the bundlebranches. No Adams-Stokes attacks have occurred since September 1926. No failure. Pulse-rate varies between 38 and 54.

(3) Male, age at death 69. History of loss of consciousness in 1915 ; in 1916 his doctor found a pulse-rate of 31, and it had remained at about that figure ever since.

He was fairly well and able to play golf until 1928, when he lost the right field of vision for one hour. At this time an electrocardiogram showed auricular fibrillation, complete block, and evidence of bundle-branch lesion ; pulse-rate 30 ; B.P. 180/100. W.R. negative ; orthodiagram : general cardiac enlargement. Moderate oedema. Died 1928.

(4) Male, age at death 79. In 1910 he gave a history of dizziness and shortness of breath of a few months' duration. History of syphilis forty-five years previously ; never had rheumatic fever. The pulse-rate was 40. B.P. 310/160. An electrocardiogram taken in 1913 showed complete block and right bundle-branch block. He was able to walk several miles in 1912, and could still do this in 1918.

There was no special alteration in his pulse-rate till 1922, when it was found to be 60. An electrocardiogram now showed that the auricle was fibrillating. Death occurred in 1924.

(5) Male, now aged 61. In 1924 he complained of headaches, trembling, and dyspnoea on exertion. B.P. 165/80. Electrocardiogram in October 1924 showed auricular fibrillation, complete block, defective conduction in the bundle-branches ; slight oedema of the feet. Orthodiagram : general enlargement of the heart. Pulse-rate, 40-55.

During the period of observation, five years, he has been able to do office work ; there has been occasional slight dizziness, but nothing more.

Some Prognostic Indications of the Electrocardiogram.

(1) *Aberrant ventricular complexes.* In considering the form of the ventricular complex in auricular fibrillation, any observations on the T-wave are frequently useless for two reasons ; first its deformation by superimposed fibrillation waves, and secondly its deformation by digitalis. This leaves the QRS group, and of the anomalous forms which this complex may assume, that in which its duration is excessive (over 0·1 second) is one of the most important ; it represents a definite lesion, since it has been shown that such a change can result, experimentally, only from interference with the bundle-branches, and is therefore taken to indicate a lesion of the branches when seen in human electrocardiograms. In some cases the widened QRS is also of low amplitude, and these curves have been thought to indicate a lesion of the terminal twigs of the bundle-branches, a condition referred to as arborization block ; more recent work has failed to confirm the view, however, and the evidence now suggests that delayed bundle-branch conduction is the cause (43) (52). It has been a uniform finding that a prolonged or 'aberrant' QRS notably diminished the expectation of life in auricular fibrillation. Willius (50), in a series of twenty-eight cases of 'arborization block' found the mortality to be 63·4 per cent. and the average time from examination till death nine months ; the corresponding figures for a larger series of cases of fibrillation with a normal ventricular complex were 36·9 per cent. and ten months. Jones (21) noted a similar effect when the QRS complex was 'bizarre'.

Excluding the cases of heart-block described elsewhere, there were four
cases in this series in which the QRS group exceeded 0·1 second.   In two the
direction of the main deflections suggested a lesion of the right bundle-branch,
one of the left branch, and in the remaining one the site of the lesion was
doubtful, the complexes being wide and of low voltage.   Three of these cases
lived for one year, on the average, from the time that the abnormal ventricular
complex was first recorded.   The fourth case is still alive after $4\frac{1}{2}$ years.   Thus
the conclusions of other observers are supported—that defective conduction
in the bundle-branches adversely affects the prognosis.

(2) *Premature contractions.*   Several authors believe the association of
premature ventricular beats with auricular fibrillation to have some significance.
Thus White (48), Cowan and Ritchie (11), Clerc and Stieffel (6), and Hart (18)
all consider that the prognosis is affected adversely by their presence.   The
first-quoted worker has gone farther, and suggests that they are analogous to
pulsus alternans with normal rhythm.   But Lewis (26) has published records
showing that alternation may occur with fibrillation, and in some twenty cases
he failed to find that this had any bearing on the prognosis.   Jones (21) found
that the presence of premature beats made little difference to the prognosis.

In any inquiry into the significance of premature beats, those appearing
when the patient is definitely under the influence of digitalis must clearly be dis-
tinguished from those which cannot be attributed to the action of this drug.
The records of four cases in which premature beats occurred, and in which no
digitalis had been taken for at least a month, have been examined.   The ven-
tricular rate was rapid in all these cases, varying from 100 to 150, and in none
of their electrocardiograms was there a depression of the R–T segment, which, if
present, would indicate the persistence of the digitalis action.   In these four
cases the average duation of life with fibrillation from the time that the prema-
ture beats were recorded was $7\frac{3}{4}$ years, which exceeds the average for all cases
irrespective of the presence or absence of premature beats, and of aetiology.   It
becomes more likely, therefore, that premature beats of the kind which occurs
spontaneously do not adversely affect the prognosis in fibrillation.

(3) *The amplitude of fibrillation waves.*   The amplitude of the waves pro-
duced by the fibrillating auricles varies considerably from patient to patient,
and also, but to a less extent in records taken from the same patient, as a result
of alterations in the plane of the circus movement with respect to the plane of
the lead.   In 1915 Hewlett and Wilson (20) drew attention to the variations in
amplitude, but attached no significance to the finding.

In any given case maximum oscillations are obtained when antero-posterior
chest leads are used.   In a series of records taken in this way from fourteen
patients, a comparison with records taken with limb leads, showed that though
the oscillations were, in general, smaller when the last were used, the difference
was not great ; and using a classification of the waves, according to amplitude,
as small, medium, and large—a purely personal standard with no exact measure-
ments, which cannot be applied to these waves—it was found that oscillations

recorded by the one method usually fell into the same category as when recorded by the other. A hundred records taken with limb leads have been analysed, and the amplitude of the oscillations considered in relation to the duration and aetiology of fibrillation. The results are set out in Table IV. This shows the size of the fibrillation waves in three groups of cases, rheumatic, non-rheumatic, and exophthalmic goitre; and where the duration of fibrillation has been reasonably ascertainable this has also been tabulated—in three periods—in relation to each amplitude group. The records show, first, that while in the majority of cases of mitral stenosis the waves are moderate, with few of either small or large, in the non-rheumatic group they are mostly small, with few moderate and only very rarely large waves. In the small number of ex-ophthalmic goitre cases the distribution in the three amplitude groups is fairly uniform. Secondly, the figures showing the duration of auricular fibrillation in three periods considered in connexion with each amplitude group hardly justify a deduction that there is any relation between duration and amplitude, except, however, that there was no case having large waves in which the duration was five years or more. A study of their size in relation to aetiology leads to one conclusion only, which is at all definite, namely, that the waves are, in general, larger in the rheumatic than in the non-rheumatic cases. This difference recalls the fact that the 'P' wave in mitral stenosis with normal rhythm may show a large amplitude. When in a case of fibrillation it is difficult to decide from clinical examination alone whether the aetiology is rheumatic or non-rheumatic, an electrocardiogram may help. If the record shows well-marked fibrillation waves the aetiology is more probably rheumatic, while if these waves are hardly dis-cernible, then it is more likely to be non-rheumatic.

TABLE IV.

Table showing the Amplitude of Fibrillation Waves (in Three Groups, 'Small', 'Medium', and 'Large') in Auricular Fibrillation of Three Types.

		Rheumatic.			Non-Rheumatic.			Exophthalmic Goitre.		
		Small.	Medium.	Large.	Small.	Medium.	Large.	Small.	Medium.	Large.
	No. of Cases.	7	46	10	14	17	2	2	2	1
Duration of Auricular Fibrillation.	1 year or less.	5	21	7	4	12	2	1	2	1
	1–5 years.	—	4	1	3	1	—	—	—	—
	5 years or more.	2	8	—	1	—	—	—	—	—

Angina Pectoris.

Auricular fibrillation seldom develops in angina pectoris; when it does so its onset usually coincides with the disappearance of pain. Similarly, it has been noted that angina often ceases with the advent of congestive failure; one explanation is that dyspnoea so curtails the amount of effort that the exertion

necessary to induce angina is never reached. Exceptions where angina persisted with fibrillation have been published (31) ; and congestive failure may in addition be present, although coronary thrombosis is excluded (4). From the work of recent years it is evident, however, that coronary occlusion is the basis of most cases where angina and fibrillation are concurrent. In one hundred cases of coronary thrombosis, paroxysmal fibrillations occurred in seven (39).

In this investigation a search for angina in hospital records of 2,000 cases of auricular fibrillation has revealed only five instances. In one, a man of 44, there was rheumatic heart disease with mitral stenosis. Pain in the third and fourth left interspaces, radiating into the left arm, occurred on movement, but the attacks were not severe ; there was no congestive failure. In the second case there was mitral stenosis with raised blood-pressure (200/110 just before the onset of auricular fibrillation). Angina of effort was present with normal rhythm and persisted after the onset of fibrillation ; again there was no congestive failure. In a third there was angina of effort in a man with right bundle-branch block. Auricular fibrillation with failure was first recognized in him eighteen months before he began to get pain. Two and a half years later he had slight oedema of the ankles ; he was able to walk short distances slowly, but his capacity for effort was limited by retrosternal pain, and not by dyspnoea.

The fourth case gave a history of effort angina for one year ; then there was an attack of coronary thrombosis accompanied by a paroxysm of auricular fibrillation, after which he still had effort angina with normal rhythm. Seven months later, after an occasional paroxysm of fibrillation, the arrhythmia became permanent. Congestive failure then appeared, but nevertheless his angina on effort persisted, and death occurred suddenly about eighteen months later. In a fifth case, effort angina, unaccompanied by failure, was a sequel of coronary thrombosis. Attacks of angina recurred till death, which was sudden, three years after the thrombosis and two months after fibrillation was first recorded.

In coronary thrombosis the advent of fibrillation has a variable effect on the pain. Thus in ten cases of thrombosis in which paroxysmal fibrillation occurred, the pain diminished or ceased in four when the pulse became irregular. In two of these four failure made its appearance with the new rhythm. In the remaining six cases pain persisted concurrently with fibrillation, congestive failure being present in two only.

The discovery of only five cases of concurrent angina and fibrillation in a series of 2,000 patients with the arrhythmia, confirms the view already widely held—that the combination is a very rare one. The presence of congestive failure in two of them, shows that simultaneous angina and congestion, while admittedly rare, is not an impossibility. In the series of ten cases of coronary thrombosis with paroxysmal fibrillation, the pain was assuaged at the onset of the paroxysm in some, but there was no relief in others. In the first group congestive failure developed with the advent of fibrillation in half the cases, but in only a third of the last group. It seems that pain is more likely to persist with fibrillation in coronary thrombosis if there is no failure.

Auricular Fibrillation and Infective Endocarditis.

Although infective endocarditis and auricular fibrillation are both, by themselves, common as sequelae of rheumatic carditis, the two conditions occur together with a remarkable rarity, which has been commented on by Libman (28), Parkinson and Clark-Kennedy (38), and by Rothschild, Sacks, and Libman (41). The last observers noted auricular fibrillation once in 109 cases of active subacute bacterial endocarditis, and here the rhythm was normal until three days before death. On the contrary, they found auricular fibrillation three times, and auricular flutter once in fourteen cases in the bacteria-free or ' healed ' stage of the disease, and they conclude that while the arrhythmia is exceptional in the active stages, its frequency when healing has occurred in no less than in chronic rheumatic valve disease. Mackenzie (32) mentions a solitary case of infective endocarditis with paroxysmal fibrillation, and one is mentioned by Wolff and White (53) in which auricular fibrillation and infective endocarditis occurred at about the same time, three years after normal rhythm had been restored with quinidine. In a series of about 1,200 cases of auricular fibrillation, infective endocarditis has been diagnosed in three, representing an incidence of 0·25 per cent. Only one of the three, who all had mitral stenosis, was a woman, and in her the infection occurred during pregnancy. Two patients came under observation with the infection and fibrillation already present, but in the third the arrhythmia occurred two days before death, and there seems to be no example in the literature in which the infection has developed in a patient already under observation with auricular fibrillation. Thus, available statistics indicate that patients with complete arrhythmia have at least one advantage—they are much less likely to be victims of this fatal infection.

Cases of Auricular Fibrillation with Infective Endocarditis.

Case 1. Female, aged 34. History of cough, shortness of breath, and swollen legs for six weeks. On admission to hospital, orthopnoea, cyanosis, and oedema ; afebrile ; heart enlarged, signs of mitral stenosis present ; rhythm, auricular fibrillation (polygram). Six months pregnant ; four days after admission twins born, one dead, the other died shortly after ; slight pyrexia followed ; uterus involuted normally. Spleen became palpable ; blood-culture positive. Death six weeks after admission to hospital ; no necropsy.

Case 2. Male, aged 39. Came under observation in 1914 with Graves's disease, auricular fibrillation (electrocardiogram) and congestive failure. History of rheumatic fever. Failure disappeared with rest. Kept under observation for eleven years, during which period he was admitted to hospital two or three times for attacks of congestive failure. In June 1925 readmitted in a very serious condition, having had increasing shortness of breath for six months. Heart enlarged ; aortic diastolic murmur ; fibrillation still present ; no oedema ; temperature 97–102° ; purpuric spots on shoulders and arms. Death five days after admission. Necropsy showed sclerotic rheumatic endocarditis of the mitral and aortic valves, and also acute endocarditis on both ; spleen infarcted.

Case 3.   Male, aged 29.   History of having 'caught a chill' one month before admission to hospital.   On examination, heart not enlarged; apical systolic murmur; pulse regular, rate 96.   Petechiae on back, swinging temperature, maximum, 103·5°; sweats; blood-culture positive.   Cerebral embolism occurred while under observation.   Four months after admission auricular fibrillation occurred (polygram).   Death three days later.   No necropsy.

Sudden Death.

There is no doubt that sudden death, although not by any means a frequent occurrence in heart disease generally, is not an uncommon complication when fibrillation is present.   Mackenzie (33) felt that it was often a result of giving an excess of digitalis.   Experimentally, when digitalis is given in toxic doses, a variety of the disorders of the heart-beat is produced, which terminates with ventricular fibrillation and the death of the animal (12).   The manner in which death occurs suddenly in patients with auricular fibrillation is similar to that occurring experimentally when the ventricle fibrillates—the patient may cry out, become pale and pulseless, perhaps gives a few gasps, and is dead.   Nevertheless, although it seems highly probable that this is the cardiac mechanism underlying a sudden death in auricular fibrillation, opinion is divided as to the importance of the part played by digitalis in bringing this about.   Heitz and Clarac (19) reported four instances, two with autopsies, and quote two others, one recorded by Hering and one by Lewis.   In the total six cases they were unable to find a common factor, but they discuss persistent thymus, excess of digitalis, and ventricular premature beats, each of which was present in two instances.   In a case recorded by Bramwell and Duguid (3) the patient appeared to be making satisfactory progress on small doses of digitalis which had slowed his ventricular rate to 70, when sudden death occurred.   In another case, recorded by Gossage and Braxton Hicks (17), the patient was running across the road when he fell dead; he was having $7\frac{1}{2}$ minims of digitalis three times daily at the time, but the ventricular rate is not stated.   At the autopsy nothing was revealed to account for the sudden death.   Clerc and Stieffel (6), make the unamplified statement that sudden death occurred in three out of twenty-one deaths in their fibrillation series.

Gallavardin (16), who believes that heart-block may be the explanation of sudden death, describes four cases of auricular fibrillation in whom there was a history of syncopal attacks, having the characters described by Adams and Stokes.   But in only one of these cases were attacks recorded after auricular fibrillation had been demonstrated; here the ventricular rate was about 84 and was never observed to fall below 60.

Observations on nine cases of sudden death.   Of eighty-six cases in this series in which death has occurred it was sudden in nine, or approximately 10 per cent.   In describing the death as sudden it is implied that it occurred almost instantaneously in a patient who was in fair health, and in whom there was no reason to expect such a fatality.   The average age at death was 38;

the aetiology was rheumatic in seven, non-rheumatic in two.   In seven cases the functional capacity was good, failure being absent, and the patients were able to walk about.   The other two were confined to bed, one had failure, but the second was progressing satisfactorily.   It is known that seven were taking digitalis, but in only one case did the daily dose exceed 45 minims of the tincture; this patient had been given a drachm and a half daily for a few days, but at the time of death none of the usual toxic effects of digitalis had manifested itself, and the heart-rate averaged 100.   Similarly in the other six cases known to be taking the drug there was a complete absence of digitalis toxaemia, and their heart-rates were being controlled at 55–100 with an average daily dose of 25 minims of the tincture.   The fact that digitalis was necessary in these cases to control the ventricular rates, but had not been given to excess, would seem to exclude Gallavardin's view that the mechanism concerned in sudden death may be an Adams-Stokes attack.   Considering next ectopic ventricular beats, these were seen in one instance only among the four patients in whom electrocardiograms were taken.   Likewise, the fact that in none of eight other patients, since deceased, in whom ectopic beats were recorded was death sudden is against the view that they are forerunners of a sudden demise.   In no case was the *QRS* complex of the electrocardiogram abnormal; in one only was aortic incompetence present.   Two necropsies were obtained, but in neither was there any obvious cause to account for the manner of death.   These results and those already published give us reason to assume that sudden death in auricular fibrillation is due to fibrillation of the ventricles, but with no clue as to why this occurs.   It is not related to the functional capacity of these chambers, judging by the patients' ability to take exercise; the electrocardiogram can give no hint of its imminence; and digitalis also must be rejected along with those other causes which have been put forward.   This mode of death is thus a complication which has to be reckoned with in giving a prognosis in auricular fibrillation, especially as there are no means of foretelling its occurrence.

Summary.

The prognosis in the two largest aetiological groups of fibrillation is considered.   The expectation of life is greater in that type which has often been referred to as the 'arteriosclerotic', but here is termed non-rheumatic, than in the rheumatic group.

The relation between age and prognosis in the rheumatic type is examined.

In mitral stenosis cerebral embolism is shown to occur as frequently when the rhythm is normal as when fibrillation is present.

When partial block is present apart from treatment, the outlook for patients with fibrillation is better.   Fibrillation of the auricle does not appear to add to the gravity of a case in which complete block already exists; when the two disorders are combined, Adams-Stokes attacks have very rarely occurred.

The prognosis is adversely affected by bundle-branch block. Premature ventricular contractions occurring spontaneously do not affect it.

The auricular oscillations of the electrocardiogram are generally smaller in the non-rheumatic than in the rheumatic type. There is little evidence of any relation between the duration of fibrillation and the amplitude of these waves.

Angina of effort, co-existing with fibrillation, was discovered five times in 2,000 patients with the arrhythmia. In coronary thrombosis the advent of fibrillation may or may not relieve the pain; relief seems more likely if congestive failure results.

Infective endocarditis and auricular fibrillation are both by themselves common sequelae of rheumatic carditis, but are very rarely combined.

Death is not infrequently sudden in auricular fibrillation; the factors so far put forward to explain this have been found inadequate in the series of cases studied.

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SOME EFFECTS OF WARM IMMERSION BATHS UPON THE CIRCULATION [1]

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Introductory.

FOR many years it has been known in a rather empirical way that immersion baths of various kinds and at various temperatures, with or without such other attributes as effervescence, produce some alteration in the circulation. Quantitative observations regarding these effects have been rather few. Those of Meakins and Davies (1), which were subsequently confirmed by Barcroft and Marshall (2) and extended by Goldschmidt and Light (3), indicated that the immersion of a limb in water as hot as could reasonably be borne (45° C.) produced a marked increase in the local blood-flow. Subsequently Dautrebande (4) showed that the immersion of a limb in this fashion produced an increase in the general circulation-rate. The previous literature on the effects of the temperature upon the circulation has been summarized by Bazett (5).

The experiments to be described below were carried out in order to ascertain whether any correlation might be found to exist between the general circulation-rate and some easily obtainable clinical measurement.

It is a considerable number of years since Erlanger and Hooker (6) brought forward experimental evidence showing that in a wide variety of conditions an increase in the general circulation-rate was associated with an increase in the pulse-rate and pulse-pressure, and that the product of pulse-rate multiplied by pulse-pressure gave an approximate indication of the general circulation-rate.

Numerous observations have shown in various pathological conditions, especially in hyperthyroidism, that there is a general correspondence between the amplitude of the pulse-pressure and the output of the heart, but there is no definite and close quantitative correlation. It was hoped in this series of experiments that some sufficiently approximate quantitative relation might be found which would enable the circulatory effects of the various kinds of baths to be determined without necessitating the somewhat complicated and laborious procedure involved in the estimation of the general circulation-rate. Although this hope was not realized, the results appear to be of sufficient interest to warrant publication. Indeed, as will be seen in detail below, in

certain cases a marked increase in pulse-rate and pulse-pressure was sometimes associated with a diminution in general blood-flow and in output per beat of the heart.

Methods.

The blood-pressure estimations were made by means of the 'Baumonometer' mercurial blood-pressure apparatus, systolic and diastolic pressure being determined by the auscultatory method. The general circulation rate was determined by estimating the carbon dioxide output per minute and the arteriovenous carbon dioxide difference. The procedure was somewhat similar to that described by Meakins and Davies (7). Modifications were as follows. The arterial alveolar air samples were obtained by Henderson's (8) automatic method, simultaneously with the collection of expired air for the estimation of carbon dioxide output. The samples of venous pulmonary air were obtained in the manner described by Meakins and Davies (7), except that prior to each re-breathing two preliminary wash-out breaths (maximal expiration and maximal inspiration) were taken from a large Douglas bag containing a mixture of approximately 6·5 per cent. carbon dioxide and 93·5 per cent. oxygen. These preliminary breaths prevented the dilution by residual air of the mixture in the re-breathing bag, and so ensured complete and almost instantaneous oxygenation of the mixed venous blood going to the lungs.

It was found that, with a simple arrangement of valves and a three-way stopcock, the entire procedure (wash-out breaths and re-breathing) could with ease be completed within fifteen to seventeen seconds. It was usually necessary to perform from three to four of these re-breathing procedures before a steady result for the venous carbon dioxide pressure could be obtained. Allowing four minutes for the analysis of the sample (taken directly into the burette of the Haldane air analysis apparatus) the venous carbon dioxide pressure could be determined with a reasonable certainty in sixteen minutes. The arterial carbon dioxide pressure and carbon dioxide output determination require a further ten minutes, so that a complete estimation of the circulation-rate can be made in slightly less than half an hour. Simultaneously with these measurements, estimations of pulse-rate, pulse-pressure, mouth temperature, and bath temperature were made by another observer. The complete observations in one experiment are shown in the protocol, which will enable the general method of procedure to be followed.

Findings, Results, and Discussions.

The detailed results representing the findings in fifteen experimental baths with three normal subjects are given in Tables I, II, and III and the protocol. The temperatures of the baths ranged from 99±1° F. to 104±1° F. (37±0·5° C. to 40±0·5° C.). The majority of the baths were with plain water, but each subject took one bath in the strong saline sulphur water.

Analysis of Strong Sulphur Bathing Water.

Specific gravity 15°	1·00293
Total solids	382·38 parts per 100,000
Sodium	138·46
Potassium	2·70
Lithium	trace
Ammonium	0·18
Magnesium	4·32
Calcium	10·33
Iron	0·25
Aluminium	trace
Manganese	trace
Chloride	200·57
Silicate (SiO_3)	1·96
Sulphate (SO_4)	5·01
Carbonate (CO_3)	50·60
Sulphide (S)	2·24

Although the subjects were never under strictly basal conditions, care was taken to have the conditions as uniform as possible. The plain water baths were taken in the bath house at the Royal Bath Hospital. This was seldom available for experimental purposes until after 4 p.m. Prior to that the subject, after a light lunch, motored or walked in a quiet leisurely way to the hospital and rested there for at least thirty minutes on a couch in the laboratory. Estimations of the normal circulation rate, blood-pressures, pulse-rates, &c., were then made. The subject then proceeded to the bath house.

Pulse-rates.

On entering a bath at whatever temperature, an immediate increase in pulse-rate was observed. This increase was most marked in the case of 'P. E.' (see Table II) on 28.8.29. His pulse-rate before entering the bath was 56; within four minutes in a strong sulphur bath it had risen to 90, an increase of 34 beats. The least rise in this subject was of 12 beats per minute, which occurred within two minutes of entering a plain water bath at 101° F. The reason for this immediate rise is not clearly apparent. It occurs before there is any significant increase in body temperature and may have been due either to some reflex effect through the cutaneous nerve-endings, or it may have been some hydrostatic effect brought about by the pressure of water. Subsequent to this initial rise there is a further increase which appears closely to follow the increase in body temperature. This would appear due to the well-known direct effect of temperature upon the sino-auricular node, for it can be demonstrated experimentally in the isolated perfused mammalian heart.

In the case of 'P. E.' (see Table II) on the 19.8.29, it will be observed that there was a further superimposed rise in the pulse-rate between 5.35 and 5.48 p.m. This rise was associated with considerable pulmonary over-ventilation, the respiratory minute volume being then more than double the normal resting volume, and the alveolar carbon dioxide pressure having fallen from 39·2 to 28 mm. Hg. The condition during this stage was obviously one of gaseous alkalosis. This condition was first described under similar circumstances (hot

immersion baths) by Bazett and Haldane (9), and it is worthy of note that the subject 'P. E.', although a medical student, had not proceeded sufficiently in his studies to be aware of the work of Bazett and Haldane, so that the hyper-ventilation which occurred during this bath can be regarded as quite spon-taneous, and the observation affords independent confirmation of the results of Bazett and Haldane on a subject who can be regarded as quite unbiased.

Blood-Pressures.

In some of the earlier baths there appears to be an immediate fall of approximately 10 to 15 mm. Hg. upon entering the bath. This, however, is due simply to posture. Ordinarily with a blood-pressure observation the subject is resting on a couch and the arm is allowed to lie by the side. If, however, the arm be lifted, as must necessarily occur when blood-pressures are taken with the subject lying in a bath, then a similar fall of approximately 10 to 15 mm. Hg. in the systolic blood-pressure is observed. The explanation of this is a matter of simple hydrostatics. Apart from this initial change, the systolic blood-pressure tends to show, if anything, an increase which may amount to as much as 20 to 25 mm., and tends to occur parallel with the increase in pulse and in body temperature.

Much more worthy of note, however, were the changes in diastolic blood-pressure. The exact diastolic blood-pressure was extremely difficult to estimate, owing to marked changes in the character of the Korotkow sounds. Wiggers (10) describes five phases in the Korotkow sounds :

'*First phase*: The sudden appearance of a clear sound, lasting for a fall of approximately 14 mm. of mercury. This has already been described as a criterion of systolic pressure.

Second phase: The acquisition of a murmurish character, lasting while the pressure falls approximately 20 mm. of mercury more. It is attributed to the stenosis of the vessel produced under the cuff at this stage.

Third phase: The replacement of the murmur by a sound becoming pro-gressively louder and lasting during the next 25 mm. pressure fall.

Fourth phase: The muffling of the sounds, lasting while the pressure falls 5 to 6 mm. more. The cause of this muffling has been variously interpreted as due : (*a*) to the absence of diastolic collapse; (*b*) to the slowing of the stream under the cuff; (*c*) to the decreased resonance in the deflated cuff; (*d*) to a lack of flattening of the arterial wall.

Fifth phase: The disappearance of all sound.'

Normally the transition from the third to the fourth phase is sharp and easily distinguishable, and it is customary to take the pressure in the sphygmo-manometer cuff at the commencement of the fourth phase as the diastolic pressure. Under the present experiments, however, after from ten to fifteen minutes in a bath at any temperature from 100° F., this clear transition point became much less obvious and difficult to detect with any degree of precision.

Almost immediately the sounds during the third phase instead of becoming

progressively louder throughout the whole phase became at first louder and then gradually softer, tailing off almost imperceptibly into the fourth phase. The interval betwen the fourth and fifth phases became progressively more and more prolonged and not infrequently after the subject had been in the bath for thirty minutes or longer sounds were audible in the artery right down to zero. In the diastolic blood-pressure columns of Tables I, II and III the left-hand figure is, so far as could be ascertained, the transition from third to fourth phase. The right-hand figure, where only two are given, is the pressure at the end of the fourth phase, that is, disappearance of all sounds. Where this figure is zero it indicates that sounds were still present in the artery when the sphygmomanometer cuff was completely deflated. Where three figures are given, the front two show pressures at which clearly defined softening or muffling of the sounds occurred. In spite of these changes and the difficulty in estimating precisely the diastolic blood-pressure, it was obvious that the diastolic blood-pressure was considerably reduced. These findings as regards Korotkow sounds and diastolic blood-pressure resemble closely those observed in such clinical conditions as severe hyperthyroidism and profound anaemia. They would appear to be associated with diminution in peripheral resistance and some alteration in arterial elasticity. A more careful analysis of the changes would necessitate the use of modern optical methods for obtaining tracings of the pulse-wave and measurements of pulse-wave velocity. Unfortunately during the present series of experiments the necessary apparatus was not available. We would suggest, however, that a more careful study of these phenomena by such methods would possibly suggest the rationale for balneotherapy in such conditions as hypertension. To summarize the blood-pressure findings it can be said that in all the experimental baths the systolic blood-pressure was maintained or somewhat increased or the diastolic blood-pressure was reduced: this means that the pulse-pressure (difference between systolic and diastolic pressure) was increased.

Circulation-rate.

In the two preceding sections it has been pointed out that with warm immersion baths there is a considerable increase both in pulse-rate and pulse-pressure. As we have already mentioned, there is a considerable body of clinical and experimental evidence that such increases are usually associated with an increase in the general circulation-rate. In the present series of experiments this was not necessarily found to be the case; although in some instances the general circulation-rate was increased, this increase never amounted to much more than 50 per cent., and is insignificant as compared with such increases as occur with even very moderate muscular work. On the other hand, in two of the experimental baths the general circulation-rate was actually diminished to a marked extent. This diminution was associated with pulmonary hyper-ventilation and considerable reduction in alveolar carbon dioxide pressure (gaseous

alkalosis). A similar diminution in circulation-rate in conditions of gaseous alkalosis has been suggested by the work of Douglas and Haldane (11) and of other observers, but so far as we are aware the present experiments provide the first quantitative observations of these phenomena which have been recorded.

It has generally been considered that the pulse-pressure, apart from conditions of regurgitation in aortic disease, is an indication of the amplitude of ventricular contraction (stroke volume of the heart). In the present experiments this was found not to be the case, and in every instance the stroke volume was found to be markedly reduced. This fact combined with the increase in pulse-rate suggests a condition resembling in a mild degree that of paroxysmal tachycardia. The most marked reductions in stroke volume were associated with hyper-ventilation and gaseous alkalosis ['J. H. H.' 27.8.29 (see Table I) and 'P. E.' 19.8.29 (see Table II)].

The full interpretation of the circulatory changes remains somewhat obscure, and one may summarize the changes observed as follows : (1) Increase in pulse-rate. (2) Maintenance or increase of systolic blood-pressure. (3) Fall in diastolic blood-pressure. (4) Marked diminution in output per beat (stroke volume of the heart). (5) General circulation-rate either normal, somewhat increased, or considerably diminished.

Provisionally, we would put forward the following tentative explanation. The maintenance of systolic blood-pressure suggests constriction of the arteries and arterioles, while the low diastolic blood-pressure would suggest considerable peripheral dilatation, presumably of the capillaries. This dilatation would give rise to a certain amount of peripheral stasis, the latter suggestion being borne out by the appearance in some instances of slight but definite cyanosis of the extremities. The increase in the pulse-rate would appear to be primary and dependent upon the action of temperature on the sino-auricular node. This increase, combined with a more or less normal or diminished venous return, would account for a diminution in stroke volume. Taking everything into consideration, apart from the temperature effect upon the sino-auricular node, the condition would appear closely to resemble a mild degree of histamine shock.

Metabolism, &c.

Figures for oxygen consumption are given in the tables, but the conditions are so complex that it is difficult to draw any conclusions from them. It is well known that an increase in body temperature is associated with an increased oxygen consumption. On the other hand, in the present experiments there are other factors which introduce complications. These are as follows:—(1) Heat retention. (2) Increase in temperature producing diminution in muscular tonus. (3) Buoyancy producing possible diminution in the amount of muscular effort required for the maintenance of posture.

In view of these considerations and the fact that the observations were not made under strictly basal conditions, it is impossible to draw any conclusion regarding the effects of baths upon metabolism.

The figures for respiratory quotients are given in order to indicate whether or not there was excessive carbon dioxide elimination.

Summary.

(1) Detailed findings of pulse-rates, blood-pressures, circulation-rates, and metabolism on three normal human subjects in fifteen different experimental baths.

(2) The pulse-rate was increased. The systolic blood-pressure either increased slightly or was maintained, while the diastolic blood-pressure was reduced, sometimes to a considerable extent.

(3) The circulation-rate showed, as a rule, a small increase, but was markedly reduced in two instances when considerable pulmonary hyperventilation and consequent gaseous alkalosis occurred.

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Table I. Subject: J. H. H.

Date.	Conditions.	Time	Systolic Blood-pressure.	Diastolic Blood-pressure.	Pulse-rate.	Mouth Temperature. °F	Bath Temperature. °F	Respiratory Minute Volume Litres.	Oxygen Consumption c.c. per min.	R.Q.	Alveolar Carbon Dioxide Pressure.	Circulation-rate Litres per min.	Systolic Output c.c. per Beat.	Remarks.
23.8.29	Lying on couch Bath 103–1° F.	p.m. 3.9–3.55	114	74	79 (?)	98.4	—	6.56	289	0.78	41.0	4.7	59 (?)	At rest in lab. room. Temp. 18.5° C.
		4.30	98	58	90	—	102							Into plain water bath at 4.33 p.m.
	"	4.35	112	48	102	101.3	103							Sweating.
	"	4.50	115	45	112	101.6	102	8.17	359	0.86	38.3	6.0	58	Legs slightly cyanosed.
	"	4.58	112	40	112	101.6	103							
	"	5.12	—	—	112	—	—							
	"	5.21	—	—	114	—	102	8.92	428	0.75	36.1	7.0	62	
	"	5.42	112	25	114	101.6								
27.8.29	Lying on couch Bath 103 ± 1° F.	3.14–4.12	110	72	60	—	—	7.15	325	0.74	38.7	4.75	79	At rest on couch in laboratory. Room temperature 19.5° C.
		4.43–5.17	114	70	60	98.2	—	7.51	306	0.78	38.3	4.76	79	Into plain water bath at 5.35 p.m.
	"	5.39	106	55–30	80	98.8	102.5							Sweating freely.
	"	5.40	100	55–35	—	—	103							
	"	5.45	114	60–40	100	—	102.8	8.14	339	0.85	39.1	6.7	63	
	"	5.50	110	65–40	102	—	103							
	"	5.53	114	65–35	108	100	103.5							
	"	5.55	114	55–30	—	—	102.8							
	"	5.59	106	55–10	110	101	103.5							
	"	6.2	116	60–20	112	101	102							
	"	6.5	110	55–20	—	—	103.5							Sounds audible in artery before pumping up armlet.
	"	6.8	118	40–0	114	101.4	103.5							
	"	6.12	118	60–0	114	—	102.6	9.66	373	0.78	29.1	3.4	30	
	"	6.18	123	70–30	120	—	103.2							
	"	6.22	117	45–0	117	—	103.2							
	"	6.25	122	45–0	117	—	103.5							
	"	6.27	113	45–0	—	101.0	—							
	"	6.30	118	50–0	116	101	103.5							
	"	6.35	120	60–0	120	101.8	103							
27.8.29	Bath 103 ± 1° F.	6.40	118	55–0	116	102	102.4							

Date	Description	Time												Remarks
27.8.29	Bath 103 ± 1° F.	6.40	118	55-0	116	102	102·4							
	,,	6.44	122	60-0	120	102	103							
	,,	6.50	122	60-0	120	—	102·8							
	,,	6.55	116	55-0	114	101·4	—							
	Bath cooled	6.58	116	60-0	108	101	102		9·20	355	0·78	33·6	6·6	56	
		7.4	94	60	90		84								
29.8.29	Lying on couch Sulphur bath 103 ± 1° F.	a.m. 10.51	118	75	52	98·1	—							At rest in dressing room. Into hot saline-sulphur bath at 11.2 a.m.
		11.4	102	60-50	92	—	108·6							
	,,	11.9	112	65-55	96		102·8							
	,,	11.13	116	60-40	100		—							
	,,	11.15	120	60-40	104		103							
	,,	11.19	118	58-40	104		103							
	,,	11.21	112	55-30	100	100	102·6		7·55	336	0·82	39·5	8·6	83	
	,,	11.24	118	56-30	112		103·2							
	,,	11.27	116	56-30	110		102·7							
	,,	11.31	118	65-30	116	100·6	102·9							
	,,	11.35	120	55-0	—		102·9							
	,,	11.40	116	65-20	114		103·3							
	,,	11.44	112	60-5	114		103		7·92	389	0·72	38·1	7·2	64	
	,,	11.48	118	60-0	114	101	102·3							Bath cooled at 11.54 a.m.
	Bath cooled	11.50	120	40-0	114	99·4	77							
		11 58	110	85	66									

TABLE II. SUBJECT: P. E.

Date	Description	Time												Remarks
19.8.29	Resting on couch	p.m. —	125	65	63	—	—		6·05	338	0·73	39·2	5·2	83	Resting on couch in laboratory. Room temperature 14° C. Into plain water bath at 4.38 p.m.
	In bath at 103 ± 1° F.	4.45	115	60	88	98·3	108							
	,,	4.52	120	60-40	96	99	103							
	,,	4.58	116	50-30	100	100	102·8							
	,,	5.3	120	60-35	108		103		8·76	385	0·82	35·4	5·9	56	Perspiring.
	,,	5.9	118	50-35	114	101·1	103							
	,,	5.15	120	45-30	116	101	102·8							
	,,	5.22	122	35-0	120	101·6	103							
	,,	5.30	126	40-0	116	102	102·8							
	,,	5.35	124	40-20	128		103		13·74	344	1·02	28·0	3·6	29	Considerable hyperpnoea, tachypnoea, and distress.
	,,	5.39	122	50-0	130		102·8							
	,,	5.45	120	60-0	129		102·8							
	,,	5.48	116	70-40	124	101·5	—							
	,,	5.51	120	60-40	120									

TABLE II (continued).

Date.	Conditions.	Time.	Systolic Blood-pressure.	Diastolic Blood-pressure.	Pulse-rate.	Mouth Temperature. °F	Bath Temperature. °F	Respiratory Minute Volume Litres.	Oxygen Consumption c.c. per min.	R.Q.	Alveolar Carbon Dioxide Pressure.	Circulation-rate Litres per min.	Systolic Output c.c. per Beat.	Remarks.
20.8.29	Resting on couch	p.m. —	106	72	62	—	—	6·66	—	—	38·8	5·65	91	In laboratory. Room temperature 15° C.
	In bath at 101±1° F.	4.25	110	?50	74	—	101·5	—	—	—	—	—	—	Into plain water bath at 4.23 p.m.
	,,	4.38	106	?42	74	98·1	100·5							
	,,	4.52	112	45–40	87	98·8	102							
	,,	4.58	114	65–30	88	99·4	101·4	7·02	344	0·75	38·7	7·8	83	Synus arrhythmia.
	,,	5.1	112	65–30	90	—	101·4							
	,,	5.7	114	55–25	100	—	—							
	,,	5.13	114	58–30	100	—	101·4							
	,,	5.20	120	50–30	100	99·7	—							
	,,	5.25	108	65–55	96	100·1	101							
	,,	5.30	116	55–30	100	100·1	100·5							
	,,	5.35	112	55–30	100	100·1	101							
	,,	5.40	114	58–38	96	—	101							
	,,	5.48	114	53–35	100	—	100·8	6·56	—	—	38·1	5·6	58	
	,,	5.52	114	56–35	100	100	101							
	,,	5.56	105	55–30	100	100·2	101							
	,,	6.3	116	58–0	92		100·4							
22.8.29	Resting on couch	—	108	58	63	98·2	—	6·71	332	0·82	39·6	6·0	95	In laboratory. Room temperature 19° C.
	In bath at 99±1° F.	4.17	116	60	78	—	99·5	—	—	—	—	—	—	Into plain water bath 4.15 p.m.
	,,	4.22	114	60	80	98·4	99·5							
	,,	4.32	118	64	84	99	98·5							
	,,	4.46	118	55–40	84	99	99·4							
	,,	4.56	114	60–45	84	99	99·1	6·50	312	0·79	37·9	6·0	72	
	,,	5.1	116	60–40	84	99	98·6							
	,,	5.5	118	60–40	88	—	99							
	,,	5.12	118	55–35	88	—	99							
	,,	5.16	118	60–40	88	99	99·2							

Date	Note	Time											
26.8.29	,,	5.22	118	60–45	88	99·1	99						
	,,	5.26	118	60–40	88	99·1	98·8						
	,,	5.31	116	60–40	88	99·2	98·9						
	,,	5.44	118	60–40	88	—	99·2						
	,,	5.48	118	60–50	88	99·3	99·0						
	,,	5.53	118	60–40	88	99·7	99·0						
	,,	5.58	114	56–40	84	99·2	98·6						
	,,	6.6	114	58–30	80	99·2	99·2	5·72	287	0·77	39·3	6·5	75
	Resting on couch	—	104	64	54	98·0	—	6·32	305	0·80	38·8	6·4	118	In laboratory. Room temperature 18·5° C.
	In bath at 103 ± 1° F.	5.28	112	50	80	98·2	103							Into plain water bath at 5.25 p.m.
	,,	5.35	106	55–40	90	—	103·2						
	,,	5.40	110	55–40	104	—	—						
	,,	5.48	116	56–20	100	100·6	103						
	,,	5.52	120	45–10	104	100·8	103						
	,,	5.57	120	50–10	106	101·1	102·4	6·95	327	0·80	39·2	9·0	88
	,,	6	126	60–20	108	101·4	102						
	,,	6.5	128	55–25	104	101·1	102·6						
	,,	6.10	126	40–0	114	—	102·8						
	,,	6.15	120	60–10	114	101·8	102·4						
	,,	6.19	122	60–10	114	101·2	102·3						
	,,	6.22	124	50–0	114	—	—						
	,,	6.38	104	44	78	—	85	8·74	308	0·91	32·7	5·0	44	Bath cooled at 6.31 p.m.
28.8.29	Resting on couch	a.m. 10.50	126	75	56	98·4	—	—	—	—	—	—	—	In dressing room.
		11.4	110	55	90	—	103·4							Into strong saline sulphur water bath at 11 a.m.
		11.8	100	60	88	—	103·2						
		11.12	102	55–40	96	—	102·8						
		11.18	108	60	—	—	—	6·18	310	0·74	38·7	5·1	54
		11.20	—	—	—	99·6	103·3						
		11.22	116	60–30	100	99·8	103							Sweating.
		11.27	120	55–20	104	100·6	102·8						
		11.33	120	40–20	104	100·8	103·8						
		11.38	124	60–20	116	—	102·9						
		11.43	118	60–0	117	—	102·3						
		11.47	118	60–5	112	101·2	102·4	8·42	384	0·77	35·0	5·4	48

TABLE III. SUBJECT: H. W. D.

Date.	Conditions.	Time.	Systolic Blood-pressure.	Diastolic Blood-pressure.	Pulse-rate.	Mouth Temperature. °F	Bath Temperature. °F	Respiratory Minute Volume Litres.	Oxygen Consumption c.c. per min.	R.Q.	Alveolar Carbon Dioxide Pressure.	Circulation-rate Litres per min.	Systolic Output c.c. per Beat.	Remarks.
8.8.29	Resting on couch	p.m. —	115	77	67	—	—	7·65	319	0·88	37·4	6·5	97	Room temperature 14·5° C.
	,,	—	111	79	62	—	—	6·44	266	0·87	37·2	6·5	104	,, ,,
	Plain water bath at 99 ± 1° F.	—	120	80	67	—	—	7·58	276	0·96	36·7	6·6	99	,, 16° C.
		—	107	61	77	—	99 ± 1	7·99	352	0·78	40·1	12·5	162	,, ,,
10.8.29	Plain water bath at 93° F.	3.40–4.15	116	68	74	—	93 ± 1	9·16	358	0·85	35·0	6·9	94	The blood-pressure figures on this day are the averages during the periods shown in column 3.
	Plain water bath at 108 °F.	4.15–5.0	116	68	73	—	—	8·16	392	0·79	34·5	6·2	85	
		5.0–5.40	125	88	104	—	103	8·31	343	0·83	31·9	4·9	47	
	,,	5.40–6.10	130	39	112	101·4	± 1 ,,	10·17	385	0·82	31·7	5·6	50	
13.8.29	Resting on couch	3.30–4.30	119	79	66	—	—	7·78	342	0·76	35·3	5·6	84	Room temperature 16·5° C.
	Plain water bath at 104° F.	5.21	111	59	80	—	104							Into bath at 5.15 p.m.
	,,	5.27	111	64	83	98·6	104							
	,,	5.39	114	55	90	99·6	103·5				34·9	6·8	78	
	,,	5.50	112	55	92	—	103·5	8·82	375	0·84				
	,,	6.0	111	54	98	101·2	104·8				33·1	7·0	71	
	,,	6.8	121	61	98	101·6								
	,,	6.14	122	65	99	—	103·4							
16.8.29	Resting on couch	4.30–5.0	120	80	70	—	—	6·56	314	0·75	36·6	6·0	86	Room temperature 18° C.
	Plain water	5.5	110	70	80	98·0	103·5							Into bath 5 p.m.

Date	Condition	Time					Bath temp.							Remarks
16.8.29	Resting on couch Plain water bath at 103° F.	4.30–5.0	120	80	70	—	—	6.56	314	0.75	36.6	6.0	86	Room temperature 18° C.
	,,	5.5	110	70	80	98.0	103.5							Into bath 5 p.m.
	,,	5.12	102	66	88	99.8	103.5	7.73	351	0.83	36.1	7.8	83	
	,,	5.20	112	66	92	—	103.5							
	,,	5.25	—	—	100	100.2	103.5							
	,,	5.32	116	68	100	—	103							
	,,	5.42	117	66	100	101	103.5							
	,,	5.47	—	—	98	101.5	102.5							
17.8.29	Resting on couch Plain water bath at 103° F.	1.0–2.22	—	—	64	—	—	7.18	341	0.74	35.2	5.7	89	Room temperature 17° C.
	,,	3.50	110	70–60	75	—	103							Into bath at 3.49 p.m.
	,,	4.0	110	65–50	80	97.5	103							
	,,	4.7	110	63–45	80	—	103.5							
	,,	4.15	120	65–50	90	—	103							
	,,	4.20	120	65–45	96	—	102.8	7.82	—	—	34.2	7.6	85	
	,,	4.27	120	60–45	96	100.2	103							
	,,	4.30	120	50–30	100	100.6	103							
	,,	4.40	120	58–30	100	100.8	103							
	,,	4.50	123	70–30	104	—	103							
	,,	4.58	126	70–30	104	—	103							
	,,	5.4	130	65–35	100	101.6	102	8.08	367	0.77	33.4	6.9	67	
	,,	5.6	—	—	104	101.4	103.3							
	,,	5.16	125	65–35	104	101.4	—							
30.8.29	Sulphur bath at 103 ± 1° F.	12.29	120	86	62	97.5							—	On couch in dressing room.
	,,	12.40	106	60	76	—	103.4							Into bath at 12.37 p.m.
	,,	12.45	106	58–40	80	—	103.2							
	,,	12.50	110	58–40	80	—	102.9							
	,,	12.55	110	60–40	90	—	103.2							
	,,	12.57	106	56–38	87	99.3	103	7.10	337	0.78	34.1	5.60	63	Loud sounds in artery at zero pressure in cuff.
	,,	1.1	112	58–0	90	100	103.1							
	,,	1.5	112	60–36–0	96	—	103.6							
	,,	1.9	110	60–38–0	96	100.2	—							
	,,	1.13	110	58–35–0	96	100.7	102.6							
	,,	1.18	120	50–30–0	93	—	102.4							
	,,	1.25	118	50–25–0	98	—	102.7							
	,,	1.28	120	40–15–0	—	—	102.9							
	,,	1.29	110	54–30–0	98	101.1	102.5	8.52	320	0.87	32.9	5.65	58	
	,,	1.35	120	60–20–0	100	101.1	102							
	,,	1.38	120	35–0	100	—	87							Loud sounds at zero. Started cooling bath at 1.39 p.m.
	,,	1.41	108	50–0	—	—	81							
	,,	1.43	104	55–20	84	—	81							
	,,	1.46	100	50–35	70	100								

PROTOCOL I.

Experiment on J. H. H., 27.8.29. (For details of temperature, blood-pressure, and pulse-rate, see Table I.)

Subject at rest on couch in laboratory since 2.30 p.m. $\left\{\begin{array}{l}\text{Temperature } 18° \text{ C.} \\ \text{Barometer 742 mm.} \\ \therefore \text{ Factor for reduction to S. T. P. 0.894.}\end{array}\right.$

Venous Pulmonary Air.

3.14 p.m.	7·08 % CO_2
3.17 ,,	7·03 ,,
3.21 ,,	7·16 ,,
3.24 ,,	7·24 ,,
3.29 ,,	7·34 ,,
3.34 ,,	7·19 ,,
3.37 ,,	7·11 ,,

$\left.\begin{array}{l}\text{Mean 7·16\% } CO_2 \\ = 49\cdot8 \text{ mm. } CO_2 \text{ pressure} \\ \text{Equivalent to } 56\cdot0 \text{ vol. \% } CO_2 \\ \text{ in mixed venous blood}\end{array}\right\}$

Alveolar Air (Henderson Automatic).

3.43–4.05 p.m.	5·60 % CO_2
4.05–4.13 ,,	5.51 ,,

$\left.\begin{array}{l}\text{Mean 5·56\% } CO_2 \\ = 49\cdot7 \text{ mm. } CO_2 \text{ pressure} \\ \text{Equivalent to } 50\cdot9 \text{ vol. \% } CO_2 \\ \text{ in arterial blood}\end{array}\right\}$

$\left.\begin{array}{l}\text{Arteriovenous } CO_2 \\ \text{difference } 56\cdot0 - 50\cdot9 \\ = 5\cdot1 \text{ vol. \%, or } 51 \text{ c.c. } CO_2 \\ \text{ per litre of blood}\end{array}\right.$

Expired Air (Douglas Bag).

Collected 4.05–4.12 p.m. (7 minutes) 56 litres
i. e. $56 \div 7 \times 0\cdot894 = 7\cdot15$ litres per minute at standard temperature and pressure.

$\left.\begin{array}{l}CO_2 \ 3\cdot41 \ \% = 242 \text{ c.c. } CO_2 \text{ expired per minute} \\ O_2 \ 16\cdot63 \ \% = 325 \ ,, \quad O_2 \text{ absorbed } \quad ,, \quad\quad ,,\end{array}\right\}$ *Respiratory Quotient*: $\dfrac{242}{325} = 0\cdot74.$

∴ *Circulation-rate* (3.14–4.13 p.m.)

$$\frac{242}{51} = 4\cdot75 \text{ litres blood flow per minute. } \text{ Pulse average 60.}$$

∴ Stroke volume of heart $\dfrac{4750}{60} = 79 \text{ c.c. per beat.}$

Venous Pulmonary Air.

4.50 p.m.	7·05 % CO_2
4.54 ,,	7·08 ,,
5.01 ,,	6·97 ,,

$\left.\begin{array}{l}\text{Mean 7·03 \% } CO_2 \\ = 48\cdot9 \text{ mm. } CO_2 \text{ pressure} \\ \equiv 55\cdot7 \text{ vol. \% } CO_2 \text{ in mixed} \\ \text{ venous blood}\end{array}\right\}$

Alveolar Air (Henderson Automatic).

5.07–5.12 p.m.	5·49 % CO_2
5.12–5.17 ,,	5·52 ,,

$\left.\begin{array}{l}\text{Mean 5·51 \% } CO_2 \\ = 38\cdot3 \text{ mm. } CO_2 \text{ pressure} \\ \equiv 50\cdot7 \text{ vol. \% } CO_2 \text{ in arterial} \\ \text{ blood}\end{array}\right\}$

$\left.\begin{array}{l}\text{Arteriovenous } CO_2 \\ \text{difference } 5\cdot0 \text{ vol. \%} \\ \text{i. e. } 50 \text{ c.c. } CO_2 \text{ per litre of} \\ \text{ blood}\end{array}\right.$

Expired Air. 5.12–5.17 p.m., 42 litres, i. e. *7·51 litres per minute* at S. T. P.

$\left.\begin{array}{l}CO_2 \ 3\cdot20 \ \% = 238 \text{ c.c. per minute} \\ O_2 \ 17\cdot04 \ \% = 306 \ ,, \quad ,, \quad ,,\end{array}\right\}$ R. Q. 0·78.

∴ *Circulation rate* (4.50–5.17 p.m.).

$$\frac{238}{50} = 4\cdot76 \text{ litres per minute. } \text{ Pulse average 60.}$$

∴ Stroke volume 79 *c.c. per beat.*

Subject entered plain water bath—temperature $103 \pm 1° \text{ F.}$—at 5.35 p.m.

Expired Air. 5.48–5.53 p.m., *45.5 litres*, i. e. 8·14 litres per minute at S. T. P.

$\left.\begin{array}{l}CO_2 \ 3\cdot57 \ \% = 288 \text{ c.c. per minute} \\ O_2 \ 16\cdot30 \ \% = 339 \ ,, \quad ,, \quad ,,\end{array}\right\}$ R. Q. 0·85.

Alveolar Air (Henderson).

    5.44–5.48 p.m.   5·62 % CO_2 = 39·1 mm. CO_2 pressure

    5.48–5.53 ,,   5·62 % ,, ,, $\equiv$ *51·1 vol. % CO_2 in arterial*
                                      blood

Arteriovenous CO_2 difference 4·3 vol. % i. e. *43 c.c.* CO_2 per litre of blood

Venous Pulmonary Air.

    5.56 p.m.   7·03 } = 6·94 % CO_2 = 48·3 mm. CO_2 pressure

    6.00 ,,   6·84 } $\equiv$ 55·4 vol. % CO_2 in mixed venous blood

  $\therefore$ *Circulation-rate* (5.44–6.0 p.m.).

       $\dfrac{288}{43}$ = *6·7 litres per minute.*   Pulse average 106.

    $\therefore$ Stroke volume 63 c.c. per beat.

Venous Pulmonary Air.

    6.07 p.m.   6·71 % CO_2 Mean 6·60 % CO_2

    6.12 ,,   6·56 ,,   = 45·9 mm. CO_2 pressure

    6.28 ,,   6·72 ,, $\equiv$ *54·4 vol. % CO_2* in mixed

    6.33 ,,   6·41 ,,   venous blood

Arteriovenous CO_2 difference *85 c.c.* per litre of blood

Alveolar Air (Henderson).

                            Mean 4·19 % CO_2

    6.17–6.21 p.m.   4·63 % CO_2 = 29·1 mm. CO_2 pressure

    6.21–6.26 ,,   3·75 ,, $\equiv$ *45·9 vol. % CO_2* in arterial
                                 blood

Expired Air (6.21–6.26 p.m.), 54 litres, i. e. 9·66 litres per minute at S. T. P.

    CO_2 3·05 % = 292 c.c. per minute } R. Q. 0·78.
    O_2 17·25 % = 372 ,,   ,,   ,,

  $\therefore$ *Circulation-rate* (6.07–6.33 p.m.).

       $\dfrac{292}{85}$ = *3·4 litres per minute.*   Pulse average 116.

    $\therefore$ Stroke volume *30 c.c. per beat.*

Venous Pulmonary Air.

    6.38 p.m.   5·95 % CO^2 Mean 6·06 % CO_2

    6.44 ,,   6·28   ,,   = 42·1 mm. CO_2 pressure

    6.48 ,,   5·95   ,, $\equiv$ 52·6 vol. % CO_2 in mixed
                                 venous blood

Arteriovenous CO_2 difference *42 c.c.* CO_2 per litre of blood

Alveolar Air (Henderson).

                            Mean 4·83 % CO_2

    6.49–6.53 p.m.   4·77 % CO_2 = 33·6 mm. CO_2 pressure

    6.53–6.58 ,,   4·89   ,, $\equiv$ *48·4 vol. % CO_2* in arterial
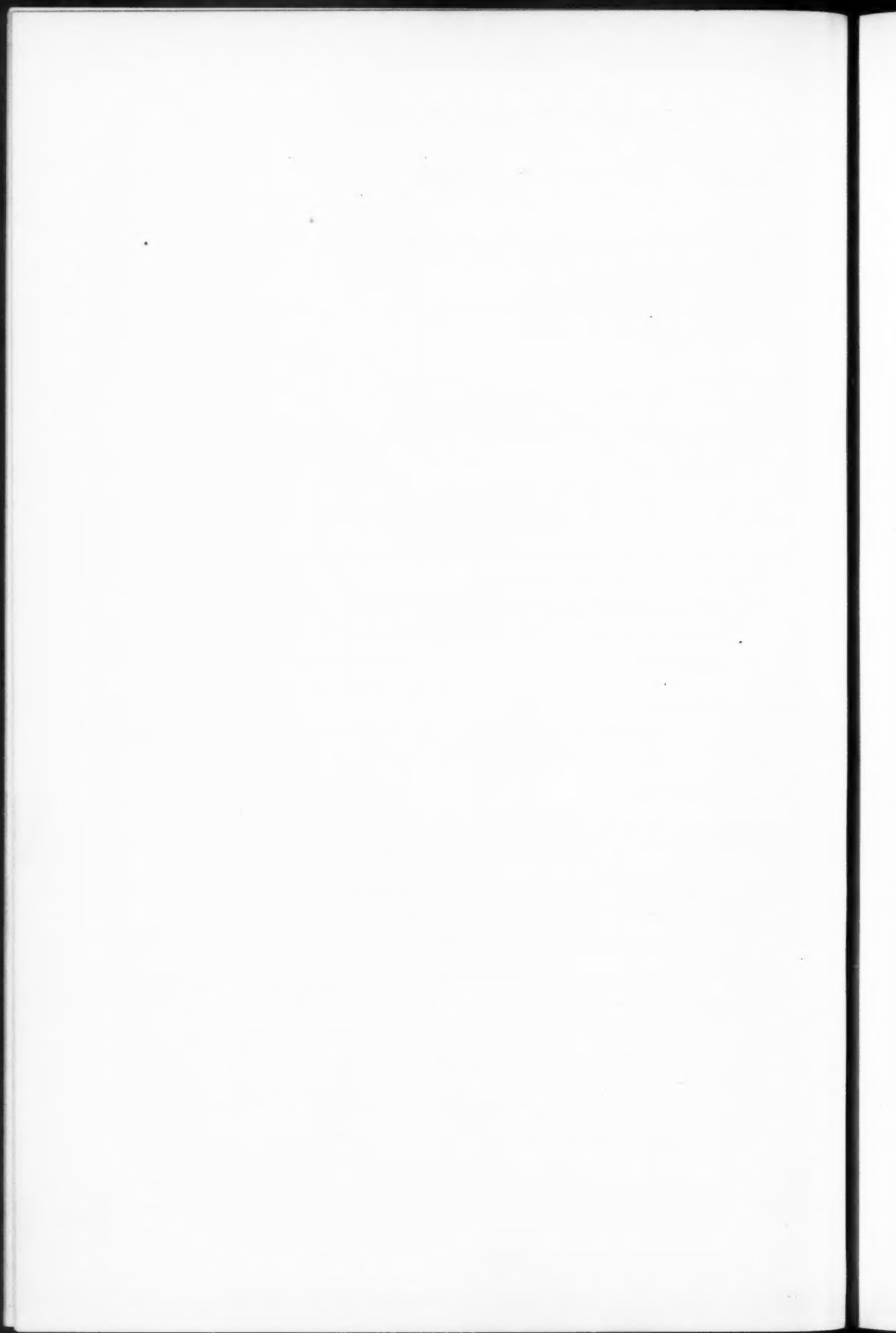   blood.

Expired Air.   6.53–6.58 p.m., 51·5 litre = 9·20 litres per minute at S. T. P.

    CO_2 3·04 % = 277 c.c. per minute } R. Q. *0·78.*
    O_2 17·25 % = 355 ,,   ,,   ,,

  $\therefore$ *Circulation-rate* (6.38–6.58 p.m.).

       $\dfrac{277}{42}$ = *6·6 litres per minute.*   Pulse average 118.

    $\therefore$ Stroke volume *56 c.c. per beat.*

CRITICAL REVIEW:
DISSEMINATED SCLEROSIS[1]

By W. RUSSELL BRAIN.

I. *Introduction.*

IT is nearly one hundred years since disseminated sclerosis was first recognized as a pathological entity. In 1835 Cruveilher, at the Salpêtrière, and almost contemporaneously Carswell, a London medical student, described the characteristic sclerotic patches in the spinal cord. Cruveilher reported the clinical features of a case, and later Frerichs' diagnoses of spinal sclerosis were confirmed at autopsy by his pupil Valentiner. The pathology of the disease was further studied by Rokitansky and Rindfleisch, who in 1863 described thickening of the vessel walls, perivascular cellular infiltration, and fatty changes in the neuroglial cells. Leyden in the same year emphasized the causal importance of exposure to damp and cold, trauma, mental stress, and antecedent infections. Then followed Charcot's great contribution to the symptomatology and pathology of the disease, Uthoff's analysis of its ocular manifestations and Marie's emphasis upon the rôle of the acute infectious diseases in its aetiology. The end of the century saw the emergence of the view that the underlying disturbance was a neuroglial hyperplasia due to an inborn abnormality of the nervous system. Pathological investigation, however, with the aid of new staining methods and a new knowledge of neuroglial reactions has traced the sclerotic plaque to its earliest beginnings. The new facts thus brought to light have relegated the striking neuroglial changes to a secondary place as the reaction to a pathogenic agent, and re-established disseminated sclerosis as an infective disease. Thence has sprung the search for a causal organism, and a renewed interest in environmental factors of possible aetiological significance.

Thus far the progressive development of scientific method has brought us, but this process is now receiving an acceleration from the unprecedented evolution of acute infective diseases of the nervous system which the present generation is witnessing. The appearance of encephalitis lethargica offered to clinical observation, pathology, and bacteriology a new impetus and opportunity for the study of neurotropic infections, to which they hardly had had time to respond when post-vaccinal encephalitis raised even more complicated problems. It was quickly recognized that encephalitis following vaccination, measles, and other exanthemata showed pathological analogies with disseminated sclerosis, which has thus been swept into the current of one of the most vigorous streams of neurological research. At the present moment, therefore, a critical review of

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disseminated sclerosis is peculiarly opportune, but its range imposes upon the reviewer a task for which perhaps no single individual is adequately equipped.

II. *Distribution and Incidence.*

1. *Geographical Distribution.*

(i) *England and Wales.* The incidence of disseminated sclerosis in the populations of various countries has been the subject of numerous statistical studies. Unfortunately owing to the dissimilarity of the methods of estimation employed these are of little comparative value. Most figures are derived from patients admitted to neurological hospitals, but they are usually expressed as percentages of cases with 'organic disease of the nervous system' or of 'total admissions'—terms which possess no constant meaning. Many such studies moreover are twenty or more years old, and hence take no account of the more modern methods of diagnosis. The following figures have therefore been obtained for the purpose of this review.

During the five years 1924–28 there were 3,438 in-patients admitted to the Hospital for Epilepsy and Paralysis, Maida Vale, London. If patients suffering from the psychoses and psycho-neuroses are excluded there were 2,449 individuals suffering from 'organic diseases of the nervous system', including epilepsy and chorea. Neurosyphilis claims 10·1 per cent. of total admissions and 14·2 per cent. of 'organic' cases; disseminated sclerosis 8·1 per cent. of total admissions and 11·4 per cent. of 'organic' cases; and encephalitis lethargica 6·8 per cent. of total admissions and 9·6 per cent. of 'organic' cases. These figures support Guillain's assertion that 'disseminated sclerosis is, after syphilis, the most frequent disease of the nervous system'.

At the London Hospital during the same five years, 1924–28, there were 33,090 admissions to medical beds, of which 116 were patients suffering from disseminated sclerosis, or 3·5 per 1,000. The Reports of the Registrar-General for England and Wales show that during the four years 1924 to 1927 the average number of deaths per annum attributed to disseminated sclerosis was 762, or approximately 20 per million of the population. The proportion of the population affected is represented by the quotient, annual death-rate × average duration of disease in years. It is impossible to assess accurately the average duration of the disease in years, and consequently there must be a considerable margin of error in estimating the incidence in the population. Bramwell's (33) figure of about eight years as the average duration, multiplied by the annual death-rate, yields an approximate incidence of 160 cases of disseminated sclerosis per million living persons in England and Wales. Wilson (211) has calculated the death-rate for each county of England and Wales for the year 1925, and finds that while the death-rate for the whole country was 17·5 per million, the county death-rate was highest in the soke of Peterborough, where it was 103·3 per million, and lowest in Middlesex, Dorset, and Buckingham, all of which had death-rates of less than nine per million.

(ii) *The United States of America.* There is abundant evidence that the incidence of disseminated sclerosis in the United States is much lower than in England and Wales. Its incidence in men drafted for service in the United States during the war was very small, the highest rate in any state being 180 per million (Davenport (50)). It must be remembered that men drafted for service were of an age at which the incidence of disseminated sclerosis is maximal, and the above rates must be considerably higher than those for the general population, which includes children and the aged. The proportion of the whole United States population affected is not likely to be more than 50 per million, a rate less than one-third of that in England and Wales. Bramwell (32) reached a similar conclusion by a different method.

The low incidence of the disease in the general population of the United States is reflected in the low proportion of admissions to neurological hospitals attributable to disseminated sclerosis. (Wechsler (209), Sachs and Friedman (164).) Wechsler states that 3.36 per cent. of 'organic cases' admitted to the Montefiore and Mount Sinai hospitals were cases of disseminated sclerosis. The corresponding figure for the Maida Vale Hospital, London, was 11.4 per cent. These figures, while of some value, are not strictly comparable, since the proportion of cases of disseminated sclerosis among hospital admissions varies with the relative frequency of other diseases, such as neurosyphilis, which probably differs in the two countries.

Some light has been thrown upon the geographical distribution of the disease in the United States by the medical examination of military drafts. (Davenport.) The highest rates among drafted men were found in Michigan, Minnesota, and Wisconsin, adjacent states bordering the Great Lakes. Outside this region the highest rates were found in the states of Washington, Mississippi, and Maine. Too much importance, however, must not be attached to these conclusions, which are derived from very small numbers.

(iii) *Other countries.* Disseminated sclerosis is common in European countries, with the exception of Italy (182) and Rumania (123). The incidence is very high in Switzerland. A recent statistical survey in the province of North Switzerland has shown that 360 per million of the population are affected, (24), more than double the assessed rate for England and Wales. In the town of Basel the morbidity rate is 740 per million. According to Veraguth (207), disseminated sclerosis is commoner than neurosyphilis in Switzerland. Monrad-Krohn (133) states that it is very common in Norway.

Outside Europe and North America it appears to be rare (182). Dr. Kooy, in a personal communication to the reviewer, states that it is very rare in South Africa. It is rare also in China, where Woods (216) found an incidence two-fifths of that in the United States, in Japan (132), (165), and Chile (193).

2. *Variations in racial susceptibility.* The United States with its heterogeneous population, comprising many races, offers exceptional opportunities for studying variations in racial susceptibility to disease. Statistical studies of the incidence of disseminated sclerosis in different races have yielded interesting

results.   Among 'drafted men ', that is, those called up for military service during
the war, the highest incidence of the disease was found among Finns and Scan-
dinavians, with rates of 29 and 16 per 100,000 men examined.   No other section
or group showed a higher rate than 10 per 100,000, and Davenport (50) considers
that the high ratios in Scandinavian and Finn sections 'are probably significant'.
Bailey (12) has investigated the incidence of disseminated sclerosis among cases
of organic nervous disease and injury in the different races of the 'drafted men '.
Whereas, for the whole group, cases of disseminated sclerosis constituted 7·4 per
cent. of cases of organic disease, the proportion was above the average in certain
races, being highest in Scandinavian, 12·5 per cent., and French, 10·7 per cent.
The Slavs, Scots, Germans, English, and Irish also showed a higher incidence of
the disease than the average.

Several American observers have pointed out that the incidence of dis-
seminated sclerosis is higher in the foreign-born than in the native-born popula-
tion.   Bailey finds that the proportion of foreign-born men in the whole group
of 'drafted men' with organic nervous disease was 9·2 per cent., while in the
group with disseminated sclerosis it was 12·7 per cent.   Wechsler finds a large
predominance of foreign-born among patients suffering from disseminated sclerosis
admitted to three New York hospitals.   Davenport has analysed the racial
incidence of the disease among 70 foreign-born patients in New York, and finds
that it is low among Russians and Italians.   English and Germans have twice as
many cases as expected, while in Swedes the rate is 2·5 times and in Norwegians
3·6 times the expectation.   The negro appears less subject to the disease than
the white.

The figures quoted indicate that there is a higher incidence of disseminated
sclerosis among foreign-born than among native-born inhabitants of the United
States, and that it is especially high in certain races, in general the north
Europeans, who exhibit a high incidence of the disease at home.   Whether
American-born members of these races show any increased susceptibility to the
disease is not apparent.

3. *Rural and urban life and occupation.*   The belief is widely held that
residence and occupation play a part in the aetiology of disseminated sclerosis,
but critical examination of the evidence indicates that there is little to support
current views on the subject.   Morawitz (135) stated in 1904 that disseminated
sclerosis was 'the most frequent organic disease of the central nervous system'
among the rural population of Wurtemberg.   But this statement, even if in itself
justified, cannot be accepted as evidence that the disease is more prevalent in the
rural than in the urban population, still less that rural residence is of any aetio-
logical significance.   Morawitz based his view upon thirty-three cases of dissemi-
nated sclerosis admitted during a period of two and a half years to the Tubingen
Clinic, which draws patients mainly from rural areas.   During the same period
twenty cases of tabes and ten cases of cerebrospinal syphilis were admitted.
Since these observations were made before the existence of the Wassermann
reaction it is possible that some cases diagnosed as disseminated sclerosis were

really cases of cerebrospinal syphilis. Another source of error is the small number of cases. These, however, are minor objections. It must be emphasized that Morawitz brings forward no evidence concerning the relative incidence of the disease in town and country. It is obvious that the relative prevalence of disseminated sclerosis compared with syphilis of the nervous system throws no light upon this point, in the absence of any data concerning the relative frequency of the latter disease in the urban and rural population. In this connexion it is of some interest that Smee (184), writing in 1901 upon comparative rates of mortality, observed that farmers, farm labourers, and gardeners had a mortality rate from nervous diseases of about one half the average, the lowest occupational mortality rate from this cause.

The United States military draft figures are important evidence bearing upon the relative incidence of disseminated sclerosis in town and country. The urban incidence rate was 12 per 100,000 men examined and was one-half greater than the rural rate of 8 per 100,000. Four large cities showed rates higher than the average for the urban population, namely, Philadelphia 23, Boston 15, New York 13, and Chicago 11 per 100,000. It would seem that in the United States the rate is lowest in the rural areas and highest in the largest cities. Bing and Reese after a detailed survey of the incidence of the disease in the province of Northern Switzerland reached the conclusion that there was no predominance of land workers among affected persons. They found that the morbidity rate in the town of Basel was 7.4 per 10,000, more than double the rate for the province of North Switzerland.

The view that wood-workers are especially liable to develop disseminated sclerosis has gained a wide currency. It appears to have been put forward first by Dreyfus (53) and has been supported by Bohmig (26).

Dreyfus analysed the occupations of 1,151 patients collected partly from the literature and partly from clinics at Strassburg and Heidelburg. He compared the frequency of different occupations in this group of patients with their frequency in the general population of Germany derived from census figures. He drew the conclusion that the disease was especially prevalent among agriculturists and that there was a high incidence among wood-workers, such as cabinetmakers. This conclusion cannot be accepted as statistically sound, the source of error lying in comparing select groups drawn largely from two localities with a standard derived from the whole country. Dreyfus's mode of investigation does not exclude the possibility that the large proportion of agriculturists and wood-workers among his patients is due to a preponderance of these occupations in the neighbourhoods from which his cases were mainly drawn, though he rejects an apparent high incidence among cigar-workers on this very ground.

Bohmig's statistical evidence of a high incidence among ironworkers, navvies, and wood-workers is equally unsatisfactory. This observer found that at Halle 16 per cent. of patients suffering from disseminated sclerosis were ironworkers and 23 per cent. navvies or wood-workers, while at Chemnitz the corresponding figures were 30 per cent. and 10 per cent. The inverse ratios of

the two groups in the two towns suggest that varying local labour conditions are responsible for the apparently high incidence in particular occupational groups. Bohmig presents no control observations.

Wilson (211) has analysed the occupations of persons dying of disseminated sclerosis in England and Wales in 1925 and considers that the results indicate an increased susceptibility to the disease in persons whose occupation brings them into contact with water. Her figures appear too small to justify her conclusions, and it is not clear whether her standards (expected deaths in the same occupations) have been corrected for the occupational mortality rate.

The best available statistical evidence, therefore, indicates that, both in the United States and in Switzerland, there is a higher incidence of disseminated sclerosis in urban than in rural populations. There is no satisfactory statistical evidence of any occupational incidence of the disease.

4. *Other environmental factors.* Steiner (190) endeavours to implicate a tick in the aetiology of disseminated sclerosis. He found evidence of contact with ticks in twenty-one out of forty-three cases, while this was present in only 10 per cent. of a control group of the same age and population class (Bevölkerungsklasse). Curschmann (49) supports Steiner's view on similar grounds. It need hardly be said that even if Steiner's figures are correct they would constitute no direct evidence against the tick which might be merely an index of another factor, occupational or otherwise, of aetiological significance. Even more speculative is Wilson's attempt to incriminate the rat as a possible carrier of the infection responsible for the disease.

5. *Hereditary and familial incidence.* The occurrence of multiple cases of disseminated sclerosis in one family has excited attention for many years, and a number of supposed instances have been reported. Simons (182) has recently reviewed the literature, but his review, which contains references to twenty-two reports, does not include all the reported cases. Some reported instances of the familial occurrence of disseminated sclerosis are now recognized to have been examples of other conditions, e.g. Pelizaeus-Merzbacher's disease, and the disorder described by Ferguson and Critchley (57). In other cases the diagnosis, in the absence of autopsy, must remain doubtful. Nevertheless the occasional occurrence of familial cases is unquestioned. In the majority of instances two siblings are affected. Affection of two successive generations is very rare, but a few examples of the disease in mother and son have been described.

The importance of the familial occurrence of disseminated sclerosis lies in its aetiological significance. In striking contrast to diseases attributable to an inherited germinal defect, multiple cases of disseminated sclerosis in one family are extremely rare compared with sporadic cases, and its occurrence in more than two members of a family, and in two successive generations, is almost unknown. These facts suggest that inherited predisposition plays no part in the aetiology of the disease, and that the occasional occurrence of multiple cases in a family is due either to chance, exposure to a common environment, or mutual infection.

6. *Sex incidence.* The male sex is more subject to disseminated sclerosis than the female in the proportion of approximately 3 to 2. Wechsler's series of cases collected from the literature contained 874 males and 631 females. Dreyfus in a similar series found 672 males and 479 females. Of Bohmig's 318 cases 58 per cent. were males and 42 per cent. females. In some small series females have predominated, but owing to the small numbers this is probably of no significance. The only important exception to the preponderance of males is the result of the statistical survey of the incidence of disseminated sclerosis in North Switzerland, reported by Bing and Reese (24). This yielded 117 males and 164 females. These figures, which constitute an almost complete reversal of the usual ratio, are large enough to suggest that the female preponderance in this series may be due to local environmental conditions, investigation of which might provide a clue to the aetiology of the disease.

III. *Pathology.*

The pathology of disseminated sclerosis is in itself a large subject with an extensive literature. In dealing with this aspect of the disease the reviewer is principally indebted to the now classical contribution of Dawson (51), the researches of Siemerling and Raecke (179), and Wohlwill's excellent review (214). The discussion of many details has had to be omitted, but an attempt has been made to present the broad outlines of the pathological changes with special reference to their bearings upon pathogenesis and symptomatology.

The pathological ' unit ' in disseminated sclerosis is a circumscribed patch of nervous tissue in which the pathological process runs a fairly well-defined course, terminating in the formation of a ' sclerotic plaque '. The sequence of changes has been established by observing patches at all stages of their development.

1. *An 'early patch'*. The distribution of the patches and their relationship to the blood-vessels will be discussed more fully later. All that need be said on this point now is that the majority of observers agree that the patch is in many cases perivascular, i. e. placed concentrically around a vessel. Tracing the changes from the centre to the periphery we find the following alterations in an ' early patch '.

The blood-vessels are dilated, but in the early stages there are few changes in the vessel walls. Capillary haemorrhages have been observed.

The perivascular spaces play a most important part in the pathological process, and in the early stages contain cells of several different types. The occurrence of lymphocytes and plasma cells in the perivascular spaces in disseminated sclerosis is now well recognized. Among recent workers Dawson alone seems to have failed to observe them. Their presence has been emphasized by G. Oppenheim (142) Lejonne, Guccione and Lhermitte (110), (116), Anton and Wohlwill (9), Siemerling and Raecke (179), Birley and Dudgeon (25), Guillain (79), and Symonds (200).

The other type of cell found in the perivascular space is the fat granule

cell, a large cell containing globules of fatty substances produced by the break-down of the myelin of the nerve sheaths.

External to the perivascular space is a concentric zone in which the myelin sheaths of the nerve fibres are severely damaged. Some have disappeared; others stain faintly, or appear swollen or granular. This zone contains pro-liferated glia cells with numerous processes, and fat granule cells lie in the tissue interstices together with a few lymphocytes. The axis cylinders for the most part persist, but may show degenerative changes, such as swelling, inequality in size, twisting, longitudinal splitting, or fragmentation.

Peripherally to the zone in which much myelin is lost is an area tran-sitional to normal tissue in which it is less completely disintegrated.

2. A 'late patch'. The late patch exhibits the end result of the changes just described.

The blood-vessels. These show hyaline thickening, and may be infiltrated with 'embryonal cells' (Lejonne and Lhermitte).

The perivascular spaces. Disappearance of the fat granule cells leaves the perivascular space dilated; lymphocytic infiltration may persist to some extent, and be associated with proliferation of the cells of the adventitia.

Demyelinization of the surrounding nerve tissue is complete and the spaces are filled with fibroglia, a condensation of the original glial meshwork. The axis cylinders are reduced in number, and some of those persisting show abnormalities, swelling, spindle enlargements, &c.

The transitional zone to normal tissue is constituted by a narrow ring rich in glial nuclei. According to Siemerling and Raecke, the smaller the patch the sharper its differentiation from its surroundings.

3. The evolution of the sclerotic patch. It is probable that the sclerotic patch is usually produced by the changes just described, passing through the stage sometimes described as 'fat granule cell myelitis'. Dawson believes, however, that the process may be much more chronic in some instances, and consist of little more than increasing glial hyperplasia with an absence of granular cells and other cellular reactions.

4. Other types of area. Rarely variations of the pathological process are observed, giving rise to atypical areas or patches, namely:

Areolar areas, in which the glial meshes are retained or distended.

Perivascular sieve-like areas: large open spaces around all the vessels in an affected area, amounting to an 'état criblé'.

The 'Markschattenberde' of the German writers, diffuse areas in which the myelin sheaths stain feebly with Weigart's stain, and so present a shadowy appearance.

5. Distribution of patches. More than one writer has summarized the distribution of the patches in disseminated sclerosis as (i) perivascular, (ii) sub-pial, and (iii) periventricular. This is a useful description from the point of view of macroscopical morbid anatomy, but for other purposes, especially that of pathogenesis, it is necessary to analyse this classification.

(i) *Perivascular patches.* The close relationship of the patches to the blood-vessels appears to have been first emphasized by Rossolimo and has received much attention and emphasis from recent writers. Dawson points out that ' the changes appear within but do not coincide with the area of distribution of the arteries '. Wohlwill also stresses this point. In the spinal cord there are two basal types, wedge-shaped and oval or round. These correspond to the distribution of the transverse and perpendicular branches of the lateral vessels of the cord. The transverse branches run in from the vaso-corona, the arterial wreath which unites the anterior and posterior spinal arteries. Corresponding to these branches are the subpial wedge-shaped areas of sclerosis with their base to the surface. Other arterial branches enter the cord and divide into a perpendicular branch running upwards and downwards. The patches corresponding to these are of an elongated oval shape and extend over several segments longitudinally. They appear circular or oval when cut transversely. The cervical and dorsal cord are more affected than the lower segments.

In the brain-stem and cerebellum the same primary forms are to be found, and in addition the cerebellum is often involved by extension from the roof of the fourth ventricle.

In the corona radiata round or oval submiliary foci occur, and in the basal ganglia round areas which appear to begin as perivascular patches around the branches of the lenticulo-striate and strio-thalamic vessels, and later fuse to form areas of irregular shape.

The cerebral cortex may be involved by patches of subcortical origin, or by surface patches, wedge- or arch-shaped, which coalesce to yield a moth-eaten appearance. In these cortical areas demyelinization often corresponds to the area of supply of the superficial vessel plexuses of the cortex. Similar changes are found in the cerebellar cortex.

(ii) *Subpial patches.* It is probable that both in the brain and cord the subpial patches constitute a variety of perivascular patch related to the distribution of vessels entering from the pial surface.

(iii) *Periventricular patches.* The predilection of disseminated sclerosis for the neighbourhood of the cerebral ventricles has been stressed by a number of observers, including some of the earliest, and has been studied more recently by Lhermitte and Guccione, Merle and Pastine (130), and Dawson (51). The whole of both lateral ventricles may be involved in periventricular sclerosis or the process may be limited to a part of one ventricle. It is most marked in the horns, especially the posterior horns. The patches nearest the ventricles have a direct and extensive relationship with the ventricular surface, and are formed of thick fibrillar bands. From these, finger-like extensions project into the surrounding white matter, e. g. the corpus callosum and corona radiata, or into the grey matter, e. g. the optic thalamus. In this way some periventricular plaques appear to be connected with the neighbourhood of the ventricle by a pedicle. The histological appearances in the periventricular patches are the same as elsewhere.

The aqueduct of Sylvius may be similarly affected and also the fourth ventricle.

Dawson comments on the fact that in spite of severe periventricular changes the ependymal epithelium is normal. But both Lhermitte and Guccione and Merle and Pastine report abnormalities in the ependyma. The former observed cysts in the ependyma of the aqueduct of Sylvius, and the latter granulations consisting of eminences of glial proliferation, and resembling the appearances found in granular ependymitis.

Two views have been put forward to explain the periventricular sclerosis. Dawson appears to accept Borst's suggestion that it is related to the rich vascularity of this region, which would bring periventricular sclerosis into the category of the perivascular lesions. Merle and Pastine believe that it is secondary to abnormalities in the cerebrospinal fluid. Lhermitte and Guccione regard both factors as playing a part. Further discussion of this point is deferred to a later section.

6. *Pathological changes in special situations.* (i) *The visual fibres.* Disseminated sclerosis may involve the visual fibres at many points. Dawson states that the optic chiasma is most frequently affected, especially its anterior border. Velter (206) notes that patches in the optic nerves are related to the central vessels, while in the chiasma and optic tracts they may be either subpial or subependymal in relation to the chiasmatic recess of the third ventricle. Dawson points out that there is marked reaction of the connective tissue as well as of the glia in the optic nerves. The whole intracranial course of both optic nerves may be devoid of myelin. The visual fibres may also be involved in the optic radiations by extensions from the periventricular sclerosis around the posterior horns.

(ii) *Cranial and spinal nerve-roots.* It is generally accepted that, as a rule, the typical patches of disseminated sclerosis are confined to the glia-bearing parts of the nervous system. Dawson examined the nerve-roots systematically in one case and found considerable variation in the extent to which demyelinization and glial reaction occurred. He considered that this variability depended upon a variability in the extent to which glia was normally present in the nerve-roots. Exceptionally, however, especially in the posterior roots of the lumbar cord, this limit appeared to be overstepped and glial proliferation to have extended far into non-glial portions of the roots. Siemerling and Raecke and Pette (151) also emphasize the frequent implication of the spinal roots.

(iii) *Peripheral nerves.* Dawson examined some of the peripheral nerves from one case with Marchi's and Weigart's strain. He found no degeneration except in the left sciatic nerve, which showed ' distinct Marchi's degeneration '. Siemerling and Raecke describe changes in the peripheral nerves, which they regard as evidence of a neuritis. They consider that these changes are not peculiar to disseminated sclerosis but are those of toxic neuritis in general.

(iv) *Meninges.* Inflammatory changes in the meninges have been remarked

by a number of workers. Dawson notes that these changes are variable. In some cases 'the pia was frequently slightly thickened, contained a slight increase of cells, and the glial vessels showed changes very similar to those within the sclerosed tissue'. When the abnormalities are more marked Dawson regards them as due to 'complications', but it is difficult to accept this view. The meningeal changes are sometimes diffuse, sometimes related to neighbouring sclerotic patches in the nervous system, and sometimes patchy, but without relation to sclerotic plaques in the brain or cord. It is interesting to note that fat-granule cells have been observed in affected areas of the meninges by Dawson and others.

✗ (v) *Secondary degeneration.* The absence of secondary degeneration in the nervous system in disseminated sclerosis was emphasized by early writers. It is now, however, recognized that this certainly occurs (Dawson, Siemerling and Raecke, Guillain, and others).

(vi) *Internal hydrocephalus.* Internal hydrocephalus in disseminated sclerosis has been described by Merle and Pastine and by Siemerling and Raecke. It is possible that atrophy of the cerebral hemispheres plays a part in its production, but it has also been suggested that it is due to obstruction to the aqueduct of Sylvius by surrounding sclerosis and ependymitis.

IV. *The Pathogenesis of Disseminated Sclerosis.*

1. *The nature of the pathological process.* Modern histological studies of the nervous system have done much to simplify the pathological problems of disseminated sclerosis. The work of Siemerling and Raecke, Dawson, and others has enabled us to trace the development of the sclerotic plaque from its earliest stages. At the same time new methods of staining neuroglia have thrown light upon the different types of glial cells and their reactions to disease and injury of the nervous system. A brief account of these neuroglial reactions is essential to an understanding of the pathology of disseminated sclerosis.

Modern staining methods have led to the differentiation of four types of glial cells—the protoplasmic and fibrous astrocytes, microglia, and oligo-dendroglia. Comparatively little is known about the behaviour of oligo-dendroglia, and for our present purpose only the three other types need be considered. The astrocytes and microglia differ markedly in their reaction to neural damage, and perhaps also in their origins. The normal functions of glia are still largely a matter of hypothesis, but there is some justification for recognizing that one of the normal roles of the astrocytes is to form a supporting tissue, anchored firmly to the blood-vessels of the nervous system by their sucker-feet: the whole system of blood-vessels and astrocytes being called by Penfield (147) 'the vaso-astral framework' of the nervous system. Penfield and Buckley (148) have studied the astrocytic reaction to neural damage. In the presence of injured nerve tissue protoplasmic astrocytes become converted into the fibrous type, and a multiplication of these occurs. If the injury to the

brain be produced by a hollow needle so that the core of damaged tissue is removed, fibroglial proliferation is comparatively slight, and the astrocytes are arranged so that their larger processes are tangential to the focus of injury. If, however, a solid needle be used, and the damaged tissue remains, there is a greater multiplication of fibroglia, the larger processes of which adopt a radial arrangement, pointing towards and away from the injured area, and resulting in a dense glial scar.

The characteristic reaction of microglia to neural damage is the conversion of the microglial cell into a phagocyte which ingests lipoid material and becomes the compound granular corpuscle, which passes by the interstices of the neural tissue into the perivascular spaces, and probably discharges its contents into the capillaries. Thus all the main features of glial hypertrophy and compound granular cell formation which are to be found in disseminated sclerosis have been observed to result from the experimental destruction of brain tissue. These facts assume importance in relation to the theories of the nature of disseminated sclerosis put forward in the early years of this century by Müller (137), Strümpell (199), Schmaus (172), and Ziegler (218). These conceptions, though not identical, possess a common feature in the view that the pathological process is essentially a hypertrophy of the glia arising from a congenital abnormality. Müller recognized, however, that in some cases this glial over-growth was precipitated by an acute infection of the nervous system, acute encephalitis or myelitis, while in other cases no such predisposing cause could be found, and he drew a number of histological distinctions between these two groups, which were subsequently distinguished by Schmaus and Ziegler as 'secondary' and 'primary' respectively. In Müller's view the demyelinization in disseminated sclerosis is a degeneration secondary to the glial overgrowth.

Müller's arguments are rejected by Wohlwill and Dawson on the following principal grounds. Histological observation does not support the distinction between primary and secondary disseminated sclerosis. Not only are there no distinctive histological features by which these groups can be recognized, but it is generally agreed that recent patches showing comparatively acute changes are to be found in the most chronic cases. These recent patches, moreover, are characterized, as we have already seen, by perivascular infiltration with lympho-cytes and plasma cells, which are widely regarded as evidence of the infective nature of the pathological process. Charcot's (39) conception of a diffuse glial hypertrophy in response to an exogenous irritant, though much more in accord with modern views, takes no account of the early stages of myelin destruction.

The principal alternative to the hypothesis that disseminated sclerosis is an endogenous glial hypertrophy implies the existence of an exogenous noxa brought to the nervous system from without. This pathogenic agent must be such as to produce circumscribed lesions, mainly if not exclusively perivascular in distribution, and attended by perivascular infiltration with plasma cells and lymphocytes. Alternative explanations of these facts have been proposed: (1) that an infective agent is present in the nervous system, and (2) that the

lesions are the reaction to a toxin, brought by the blood stream or by some other route. Many recent workers, amongst others Lejonne, Guccione and Lhermitte (110), Guillain (77), G. Oppenheim (142), Siemerling and Raecke, Birley and Dudgeon, and Symonds have stressed the perivascular and meningeal infiltration as almost conclusive evidence of the infective nature of the disease. This view is reinforced by other weighty arguments. Apart from the nature of the cellular reaction it is difficult to ascribe to a toxin changes at the same time so widespread and yet so focal. The cardinal feature of the effects of toxins, whether endogenous or exogenous, upon the nervous system are (1) diffuseness, limited by (2) a certain selectivity, and (3) symmetry both in distribution and chronology. These points are well illustrated by the various forms of polyneuritis. The patches of disseminated sclerosis are circumscribed, involve all parts of the central nervous system with little discrimination, are only superficially symmetrical in distribution, and highly irregular in their chronological development. Further, we are now familiar with several forms of encephalitis, acute disseminated encephalitis, and encephalitis complicating vaccination and the exanthemata, which are generally recognized as due to infective agents, and which produce pathological pictures in many respects similar to the acute phase of disseminated sclerosis. The hypothesis of a toxic origin has the weighty support of Dawson and of Anton and Wohlwill (9), but the evidence appears to be more in favour of the view that disseminated sclerosis is due to a neurotropic infection and is an encephalo-myelitis, character-ized pathologically by perivascular demyelinization and clinically by its relapsing tendency.

Hassin's (83) revival of the older conception of disseminated sclerosis as a primary periaxial neuritis is based upon his observation of degenerative changes in the myelin sheaths outside the plaques, and a denial of the perivascular dis-tribution of the latter. Such degenerative changes as Hassin describes seem more likely to be secondary than primary, and his rejection of the perivascular distribution of the plaques is at variance with the findings of the majority of modern pathologists.

2. *Which tissue is primarily affected?* There has been much discussion as to which tissue element is primarily affected by the pathogenic agent. Redlich (156) and Hüber (93) believe that the nerve fibre is first attacked, and Marburg (119) and Mott (136) emphasize the primary susceptibility of the myelin sheath. Dawson also states that ' the most constant and uniform change is the absence of the myelin sheath'. Other observers, however, consider that the blood-vessels or the perivascular spaces are first involved and that changes in the neural elements are secondary. Thus Rindfleisch (160) believes that chronic inflammation of the vessel walls produces nutritional effects upon the surrounding tissues, and Ribbert (158) attributes a similar effect to thrombosis. Siemerling and Raecke have observed capillary haemorrhages. Borst and Schmaus consider that inflammatory adhesions in the perivascular spaces lead to lymph stasis. On the other hand, Bielschowsky (23), Taylor and Marburg

believe that the noxa passes through the vessel walls without damaging them, and that the vascular changes are secondary. We have already discussed the view that the glial reaction is the primary change.

These attempts to find a locus minoris resistentiae to the noxa of disseminated sclerosis are somewhat academic, for it seems impossible to do more than speculate whether the reaction of a certain tissue element is to the hypothetical infection or to the products of the destruction of other cells. Probably both factors operate. Nevertheless, some negative conclusions can be drawn from the facts. Although vascular changes, described above, are present both in recent and in older plaques, it seems very improbable that these are of such a character as to render the changes in the surrounding tissues attributable solely or mainly to 'nutritional disturbances'. Nor is there sufficient evidence of adhesions in the perivascular spaces to lead us to suppose that lymph stasis plays an important part (Dawson). The constancy of degeneration of the myelin sheaths indicates their high susceptibility to the noxa, and Dawson regards the glial reactions as being the response in part to the pathogenic agent, in part to tissue damage. The same may well be true of changes in the axons and the blood-vessels.

3. *The route of infection of the nervous system.* At first sight the perivascular distribution of many of the patches in the nervous system suggests a haematogenous origin of the infection, just as periventricular sclerosis suggests the cerebrospinal fluid as the source. We have already seen that there is an alternative explanation of the latter phenomenon. The same is true of the former. Recent studies of the perivascular spaces have shown them to be extensions of the subarachnoid space surrounding all vessels entering the nervous system and subdividing to clothe their branches in a similar fashion, thus reaching the pericellular spaces in the grey matter and the interfibrous spaces in the white. The perivascular distribution of a patch therefore is capable of more than one explanation. It is probable that no pathogenic agent brought to the nervous system by the blood-stream can avoid passing through the perivascular space. But a perivascular distribution would also be attained by a noxa which ascended the perivascular space from the cerebrospinal fluid of the subarachnoid space. This is difficult to accept as a likely explanation of isolated patches deeply situated in the central portions of the cerebral hemispheres, but it is probable that once a particulate virus has been brought to any situation by the blood-stream the perivascular spaces play an important part in the diffusion either of the virus itself or of its toxins.

Allusion has already been made to differences of opinion concerning the interpretation of periventricular sclerosis. Borst regards this as a confluence of perivascular patches situated around the rich subependymal venous plexus. Merle and Pastine admit the perivascular distribution of the lesions, but explain them as due to the invasion of the venous perivascular spaces from the ventricles by a noxa which reaches them in the cerebrospinal fluid. They offer experimental evidence of the continuity of these spaces with the ventricles and

describe abnormalities in the ependyma resembling a granular ependymitis which they ascribe to the action of the pathogenic agent in the fluid. Dawson, influenced by his inability to discover ependymal changes, accepts Borst's view. Lhermitte and Guccione describe a case in which periventricular sclerosis was found around one occipital horn and round the aqueduct of Sylvius. In the latter situation only was the ependyma abnormal, cysts being present. These authors consider that the affection of the occipital horn was haematogenous, but that the neighbourhood of the aqueduct of Sylvius had been infected from the cerebrospinal fluid.

It is indeed probable that both blood-stream and cerebrospinal fluid play a part in the spread of the disease. Haematogenous infection probably leads to invasion of the perivascular spaces and hence of the subarachnoid space. On the other hand, if the periventricular sclerosis is secondary to the presence of the virus in the ventricular fluid the latter has probably been infected by way of the blood-vessels of the choroid plexuses.

McAlpine (126) discusses the predilection of the virus for the optic nerves and considers that it may be due to extension of infection either from the ethmoidal cells, as Behr (19) also suggests, or (2) from the cerebrospinal fluid in the optic subarachnoid space. (3) Alternatively the optic nerves may for some reason be specially susceptible to the virus. He favours one of the first two explanations. A further route of infection of the optic chiasma from the cerebrospinal fluid, as Velter points out, is through the ependyma of the chiasmatic recess of the third ventricle.

4. *Precipitating factors.* In the earlier literature of disseminated sclerosis considerable importance was attached to factors which were believed to precipitate the onset of the disease, especially trauma, exposure to cold, and antecedent infections. It is perhaps significant that nowadays these predisposing causes receive little attention.

Marie not only at an early date proclaimed the infective character of disseminated sclerosis but regarded it as a complication of a large number of infective diseases. To-day the general recognition of the specific character of the disease has reduced such precedent illnesses to precipitating factors only, and even as such their importance is much disputed. The strongest advocates of a causal relationship between such diseases as the exanthemata, acute rheumatism, influenza, enteric fever, and disseminated sclerosis can only claim that such an association occurs in about 25 per cent. of cases. (Jelliffe, 28 per cent., Roper (162) 22 per cent., Klausner (99) 20 per cent.) Other observers give much lower figures. (Morawitz 6 per cent., Hoffmann 5 per cent.) Barker (14) states that if only those cases are included in which an acute infection preceded the onset of the disease by two or three months the statistics of the literature show such a relationship in only 3 to 5 per cent. of cases. Some authors (Woodbury, Gill, and Bassoe) impugn tonsillar and dental sepsis, infections so banal that they might be regarded as the cause of most diseases. The current widespread recognition of encephalo-myelitis as a complication of the

exanthemata and other infections suggests that such conditions may not always in the past have been distinguished from disseminated sclerosis, in the supposed causation of which these infections thus assumed a false importance. Nevertheless the recognition of pathological similarities between disseminated sclerosis and these acute forms of encephalitis should keep open the mind of the clinician to the possibility that the former disease also may sometimes be precipitated by an antecedent infection. In view, however, of the frequently slow and insidious onset of disseminated sclerosis such a relationship would be very difficult to prove.

It is perhaps hardly necessary nowadays to add that syphilis plays no part in the aetiology of disseminated sclerosis. The Wassermann reaction and increasing clinical knowledge have permitted the differentiation from the latter of these forms of neurosyphilis which were formerly confused with it.

The aetiological role of intoxications, especially metallic poisoning, has been stressed by Oppenheim. In the section dealing with occupational incidence we have seen that there are no grounds for supposing that the occupational handling of metals is a causative factor, and, as Barker points out, the disease is common in women who are not exposed to metallic intoxication. Probably the idea arose from the confusion with disseminated sclerosis of the symptoms of such intoxications as manganese and carbon monoxide poisoning.

The aetiological significance of trauma when it precedes the apparent onset of disseminated sclerosis is a difficult question of some medico-legal importance. The following possibilities must be considered: (1) that the association is a coincidence; (2) that traumatic lesions of the nervous system may be mistaken for disseminated sclerosis; (3) that trauma may induce changes in the neighbourhood of pre-existing but hitherto latent plaques of disseminated sclerosis and so lead to the appearance of symptoms; (4) that a patient after spending some time in bed as a result of the trauma may manifest symptoms because he has lost the power to compensate for a defect, such as inco-ordination of the lower limbs, due to previously-acquired disseminated sclerosis; (5) that the trauma (e.g. a fall) may be the result of pre-existing symptoms of disseminated sclerosis (e.g. inco-ordination); (6) that the trauma may produce a lesion of the nervous system (e.g. contusion) which may afford a locus minoris resistentiae for the development of the virus of the disease, hitherto latent.

Some writers would attach aetiological significance only to a trauma which preceded the onset of the symptoms of the disease by two or three months, but in view of the frequently insidious onset of disseminated sclerosis this limitation seems unjustifiable and might be extended to a year or longer. No author maintains that trauma is a possible aetiological factor in more than about 10 per cent. of cases (Hoffmann). In a given case the clinician must reach his conclusion after considering the various possibilities outlined above. It would be rash to deny the possibility of a causal relationship between trauma and disseminated sclerosis, and perhaps equally rash to assert it.

Exposure to cold, heat, and electric shock have also been invoked as

precipitating factors. These ideas antedate the recognition of disseminated sclerosis as a specific disease. Much that has been said concerning trauma applies to these hypothetical factors also, with the addition that the evidence in favour of their importance is even scantier.

V. *Experimental Transmission and Bacteriology.*

Since Bullock, in 1913, first claimed to have transmitted disseminated sclerosis to animals a considerable number of experimental and bacteriological investigations have been carried out on this subject. It will be convenient to describe separately (1) those with positive and (2) those with negative results.

Positive Observations. (i) *Experimental and bacteriological.* Bullock (36), in 1913, injected cerebrospinal fluid from a case of disseminated sclerosis sub-durally into a cat and subcutaneously into a rabbit. The cat was unaffected, but the rabbit became completely paralysed and was killed on the sixteenth day after injection. This animal is said to have shown oedema, congestion and fragmentation of myelin sheaths, in the spinal cord. The same specimen of cerebrospinal fluid after being kept on ice for fourteen days was used to inject three more rabbits, two of which remained unaffected, while the third became paralysed but recovered. A further specimen of spinal fluid from the same patient was divided into two parts, one of which was passed through a porcelain filter. Both filtered and unfiltered fluid produced paralysis after injection into two more rabbits. The spinal cord of one of these is stated to have shown extensive degeneration when stained by Weigart-Pal, and Marchi's methods. In fact 'histological examination of the spinal cord reveals a complete reproduction of the appearances found in the human subject'. From these experiments Bullock concluded that either a filterable virus or a water-soluble poison was present in the cerebrospinal fluid in disseminated sclerosis.

In the following year Steiner (189) endeavoured to repeat Bullock's experiments, and following the intradural injection of cerebrospinal fluid into a rabbit the animal became ill and died in six weeks. Kuhn and Steiner (103) carried out further experiments in 1917. They injected by various routes a series of rabbits and guinea-pigs with blood, cerebrospinal fluid or a mixture of both, obtained from thirteen patients suffering from disseminated sclerosis. A large proportion of animals developed paralytic symptoms following these injections, guinea-pigs proving more susceptible than rabbits, and blood more effective than cerebrospinal fluid. Kuhn and Steiner claimed to have transmitted the disease from one animal to another in a series of four guinea-pigs and two rabbits. Control experiments were negative. The most important result of this investigation was the authors' observation of spirochaetes in the heart's blood and the vessels of the liver of affected animals. They describe these organisms as delicate and slender, resembling those of spirochaetosis ictero-haemorrhagica, and often possessing a terminal nodule or cilia. Kuhn and

Steiner named this spirochaete, *Spirochaeta argentinensis* (Argentoratum being the Latin name of Strassburg, where their researches were carried out).

Steiner (191) at the same time inoculated a monkey, *Macacus rhesus*, intracerebrally with cerebrospinal fluid from a case of disseminated sclerosis. The animal showed no symptoms for eleven months, when it developed a transitory paresis of the lower limbs. Five months later it was killed, and Steiner found in the cerebral hemispheres plaques visible to the naked eye which histologically exhibited demyelinization, infiltration with compound granular cells, glial overgrowth, and relative survival of the axis cylinders—appearances which he considered indistinguishable from those of multiple sclerosis in man.

Simons (181) in 1918 induced weakness and, in one instance, death in rabbits by subdural and subcutaneous inoculation of cerebrospinal fluid. Macroscopic and bacteriological examinations were negative.

Marinesco (123) in 1919 observed motor weakness in two guinea-pigs injected intracerebrally with cerebrospinal fluid which produced no effects in other guinea-pigs when injected intraspinally or intraperitoneally. Spirochaetes were found in cerebrospinal fluid obtained from the affected animals by puncture of the fourth ventricle. This fluid, however, produced no ill effects when injected into other animals.

Kalberlah (96) in 1921 reported the presence of spirochaetes in the blood and tissues of rabbits which had received inoculations of cerebrospinal fluid and blood from patients with disseminated sclerosis. These spirochaetes were said to be plumper than *Treponema Pallidum*.

Gye (81), (formerly Bullock), in 1921 repeated his investigation of 1913 on a larger scale. He obtained cerebrospinal fluid from twenty-one patients with disseminated sclerosis and inoculated by various routes 129 rabbits and 15 guinea-pigs. The latter were unaffected, but 17 rabbits became ill and paralysed, usually in a few days. Similar symptoms were produced by passage of material from affected to normal animals in a few instances. No control experiments were carried out and no histological examination of the nervous systems of affected animals was made. Gye concluded that ' disseminated sclerosis is probably an infectious disease and that the virus may sometimes be found in the cerebrospinal fluid '. He found no evidence that the pathogenic agent was a spirochaete.

Pettit (152) in 1922 reported the observation of spirochaetes in the cerebrospinal fluid of two patients with disseminated sclerosis. A monkey was inoculated intraspinally with cerebrospinal fluid from a case of disseminated sclerosis, and six days later spirochaetoid bodies were found in the cerebrospinal fluid of the animal, which died in coma on the twelfth day after inoculation. Spirochaetes were similarly found in the cerebrospinal fluid of inoculated rabbits. Passage to other rabbits was sometimes obtained. Pettit cautiously concludes, however, that the pathogenic significance of the spirochaetes was not established. Similar results were reported by Stephanopoulo (195), by Sicard, Paraf and Lermoyez (176), by Schlossmann (170), and by Jensen and Schroeder (94).

Adams and his collaborators have also reported positive results of experi-

mental inoculation of animals. Adams (2) in 1921 observed nervous symptoms in rabbits following inoculation of blood and cerebrospinal fluid from cases of disseminated sclerosis. Transmission from one animal to another was obtained in two cases. No histological observations were reported. In 1924 Adams, Blacklock, Dunlop and Scott (3) repeated these experiments on a larger scale. Cerebrospinal fluid and blood from cases of disseminated sclerosis produced nervous symptoms in fourteen out of forty-two inoculated animals. In some instances 'spirochaete-like structures' were found in the tissues of rabbits which had been inoculated with cultures of blood from a case of disseminated sclerosis. The blood before inoculation was incubated in Noguchi's medium for fourteen days. 'Spirochaete-like structures' were seen in seven out of the forty-two rabbits inoculated. They were coarser and thicker than *Treponema pallidum*, and stained well by Fontana's method and by Becker's carbol-fuchsin method. All attempts to culture these spirochaetes failed. Microscopical examination revealed round cell infiltration and haemorrhages in the nervous systems of some of the inoculated animals which had exhibited nervous symptoms, but similar changes were also observed in some which had shown no symptoms. One animal showed degenerative changes in the myelin sheaths. Seven control animals were inoculated with blood and cerebrospinal fluid from normals or from patients with other diseases, but showed no symptoms. The authors concluded that the infective agent of disseminated sclerosis appeared to be present in the blood and spinal fluid of the patients, but they were unable to decide the significance of the spirochaetes found in some inoculated animals.

Adams, Blacklock and McCluskie (4) in 1925 reported the discovery of spirochaetes in the cerebrospinal fluid of two monkeys inoculated with material from cases of disseminated sclerosis. But one monkey was killed because it was dying of peritonitis due to a coliform bacillus, and in the second animal only one spirochaete was observed.

The most recent claim to have isolated the organism of disseminated sclerosis is that of Chevassut and her collaborators (40). By culturing the cerebrospinal fluid in a special medium, Hartley's broth, to which human blood serum had been added, she claims to have grown minute spherical bodies, to some of which granules are attached. These bodies, to which the name *Spherula insularis* has been given, have been cultivated from the fluid of 176 out of 188 cases of disseminated sclerosis in all stages of the disease, and have been absent in 269 controls. They require a special microscopical technique for their demonstration, and they have been found only in cultures of the fluid and not in the fluid itself. They are said to ferment glucose, laevulose, and mannitol, and the granules can pass through certain collodion membranes. Braxton-Hicks, Hocking, and Purves-Stewart (34), have endeavoured to infect monkeys with cultures of the virus by intravenous and intracisternal injection. Seven animals were thus inoculated. One subsequently developed paresis of the limbs. Histological examination of its spinal cord showed areas of ascending degeneration in one posterior column and one direct cerebellar tract. Another

animal which had appeared normal also showed degeneration in one antero-median and both lateral columns. The other animals showed neither functional nor pathological abnormalities, though some of them appeared to harbour the virus in the cisternal fluid for some time. The authors state, ' It is not claimed that these lesions are disseminated sclerosis, but their presence is suggestive '. Hocking, as a result of biochemical studies, finds that cerebrospinal fluid containing the virus exerts a specific hydrolytic action, not only upon proteins and their disintegration products, but also upon the fatty constituents which occur in nervous tissue.

(ii) *Histological in man.* The reported observation of spirochaetes in the cerebrospinal fluid of patients with disseminated sclerosis and of inoculated animals naturally led to a search for similar organisms in the nervous systems of affected patients. Siemerling (177) in 1918 reported that he had observed four or five living spirochaetes in two preparations from the brain of a patient, using the method of dark-ground illumination. Buscher (37), using the same method, reported spirochaetes showing undulatory movements fifteen and thirty-nine hours after the death of the patient. Speer (188) has made similar observations. None of the authors found spirochaetes in stained sections. Schuster (173), however, reproduces microphotographs exhibiting numerous spirochaetes in sections from the nervous system of a patient reported to be suffering from disseminated sclerosis, but who was stated to have a $\pm$ Wassermann reaction in both blood and cerebrospinal fluid. Jensen and Schroeder (94) have observed ' fibrilles spiralées ' situated intranuclearly in the cells near the central canal of the spinal cord in two cases. Steiner (194) has recently (1928) presented evidence of spirochaetes in the nervous system of a case, and lays stress on the presence of silver-staining debris, which he considers to be spirochaetal degeneration products.

2. *Negative results.* Numerous observers have described negative experimental results. Among these are: Siemerling and Raecke (179), Hauptmann (84), Olsen (141), Church (41), Guillain, Jacquet and Lechelle (80), Rothfeld, Freund and Hornowski (163), Birley and Dudgeon (25), Magnus (118), Teague (201), Achard (1), Claude, Schaeffer and Alajouanine (44), Guillain and Laroche, Noguchi (45), Marquézy (124), Stevenson (198).

Space does not permit an account of all these negative experiments. Certain investigations, however, are of special interest. Teague's research was conducted on a large scale, 200 animals being inoculated from sixteen cases, an average of fourteen animals from each patient. The animals used were guinea-pigs, rabbits, rats, mice, cats, dogs, and monkeys, all with negative results. The only unsatisfactory feature of this investigation was the small number of intracerebral inoculations performed. Birley and Dudgeon, however, obtained negative results from intracerebral and intraspinal inoculations, and so also did other workers, including Noguchi.

As examples of negative bacteriological examinations the researches of Birley and Dudgeon and of Noguchi will be described. Birley and Dudgeon

performed the following investigations. In 33 cases the fresh cerebrospinal fluid was precipitated with absolute alcohol and the deposit stained with Giemsa. In 27 cases the fluid was cultured anaerobically—in Noguchi's fluid medium (23 cases), ascitic fluid and human red cells (3 cases), Noguchi's solid medium (2 cases) and ascitic fluid only (1 case). The deposit in the Noguchi tubes after inoculation and incubation was stained with Giemsa (25 cases). Aerobic cultures were made in 19 cases, various media being used, such as litmus milk, inulin, inulin plus serum, Besredka, with and without human red cells, &c. In a few cases a diphtheroid bacillus and in one case *Staphylococcus albus* were grown, but no significance is attached to these. With these exceptions cultures remained sterile and examination of films was negative.

Noguchi's investigation is of special importance in view of his extensive researches into spirochaetal infections. He employed blood and cerebrospinal fluid from patients with disseminated sclerosis with which he inoculated 'ascitic fluid tissue medium, such as that employed for the cultivation of *Treponema pallidum* and other anaerobic treponemes, also the medium used for growing relapsing fever spirochaetes, and Leptospira medium'. Noguchi states that 'repeated dark-field examinations of the blood and cerebrospinal fluid, while perfectly fresh, failed to reveal any spirochaetes. Most of the culture-tubes remained free from ordinary contaminations, but no spirochaetes were found in any of them. Injections of the contents of the culture-tubes into guinea-pigs and rabbits produced no symptoms of significance. Dark-field examination of peripheral or heart blood of the inoculated guinea-pigs and rabbits showed no spirochaetes'. No spirochaetes were found in emulsions of liver, spleen, kidney, suprarenal glands, lymph nodes and brain of inoculated animals.

Failure to find spirochaetes in the cerebrospinal fluid from cases of disseminated sclerosis has been reported by André Thomas (8) in two instances and by Barré (16) in five. Claude's (43) observations are of considerable interest. Pettit (152) reported the presence of spirochaetes in the cerebrospinal fluid from a case of disseminated sclerosis. Claude performed the autopsy on this patient and failed to demonstrate spirochaetes in the nervous system histologically, while inoculation of rabbits with emulsions of the spinal cord proved negative. Bertrand (22) also reports negative results.

Discussion of experimental and bacteriological results. The positive results reported by investigators of the bacteriology of disseminated sclerosis may be classified as follows : (1) Evidence for the transmission of disseminated sclerosis to animals. (2) Evidence for the presence of spirochaetes (*a*) in the cerebrospinal fluid, blood and tissues of inoculated animals, (*b*) in the cerebrospinal fluid, and (*c*) in the nervous system of patients affected with the disease. (3) Evidence that the *Spherula insularis* of Chevassut is the causal organism. The validity of these contentions must now be considered.

Spontaneous infections of experimental animals. Any claim to have transmitted a neurotropic infection to animals, especially to rabbits, requires to be criticized in the light of modern knowledge of the spontaneous diseases

involving the nervous system to which these animals are liable. It is only during the last few years that the characteristics and wide distribution of such infections have been recognized, and their prevalence has necessarily led to a reconsideration of the validity of much experimental work. Three animal infections especially require consideration in connexion with the experimental transmission of disseminated sclerosis—(1) *Encephalitozoon cuniculi*, (2) *Toxoplasma cuniculi*, and (3) *Spirochaeta cuniculi*.

1. *Encephalitozoon cuniculi*. Bull (35) in 1917 first expressed the suspicion that certain inflammatory changes which he found in the nervous system of rabbits following experimental inoculations might have been present before the experiment. Further studies by Oliver (140), Wright and Craighead (217), Twort and Archer (204), and McCartney (128) confirmed these suspicions, and the organism responsible was identified and studied by Levaditi, Nicolau, and Schoen (114) in 1924, and was named by them *Encephalitozoon cuniculi*. It is a protozoan parasite, belonging to the Microsporidia, and produces lesions in the brain, kidneys, liver, and spleen. The lesions in the nervous system consist principally of infiltration with round cells, which may be found in the perivascular spaces, in the meninges, diffusely in the cerebral tissues, and beneath the ependyma of the lateral ventricles; and in a proportion of cases is associated with focal necroses, surrounded by glial hyperplasia. Cyst formation occurs at one stage in the life cycle. The organism can be transmitted from one animal to another by various routes, caged animals probably infecting each other by the urine. McCartney found the inflammatory changes present in the nervous system in 55 per cent. of 372 laboratory rabbits, none of which had received intracerebral inoculations. Oliver found similar changes in the brain in 20 per cent. of 'normal' rabbits, including animals bought at the market, and pointed out that there might be no symptoms of the disease. It is important to note that Levaditi's stock of the Encephalitozoon was derived from two animals which died following experimental inoculations.

An organism which may be present without symptoms in more than half of a stock of rabbits, which produces inflammatory changes in the brain, and may be roused into activity by intracerebral inoculations, is clearly a potential source of grave error in experimental work. Levaditi, Nicolau and Schoen (114) claim to have demonstrated that the virus which Thalhimer and Kling and his associates believed they had transmitted to rabbits from patients suffering from encephalitis lethargica was the *Encephalitozoon cuniculi*. They state further that the disease occurs spontaneously in mice, and that rats and dogs are susceptible, and possibly also guinea-pigs.

2. *Toxoplasma cuniculi*. Our knowledge of the *Toxoplasma cuniculi* is of more recent date even than of the Encephalitozoon. This organism has recently been studied by Levaditi, Sanchis-Bayarri, Lépine and Schoen (115). The Toxoplasma is an intracellular protozoan parasite to which rabbits, mice, pigeons, and young fowls are susceptible. Rabbits are most readily infected by injection intracerebrally or into a peripheral nerve. Following intracerebral inoculation

the disease usually runs an acute course, and the rabbit dies in from eight to twelve days with symptoms of encephalo-myelitis. As in the case of *Encephalitozoon cuniculi* cyst formation occurs in the developmental cycle, and the histological reaction of the nervous system is an infiltration with round cells which is both diffuse and perivascular. It is noteworthy that Levaditi's original stock of the virus was derived from two rabbits ' contaminated spontaneously ', as a result of intracerebral inoculation of ' apparently non-virulent material '.

3. *Spirochaeta cuniculi*. The hypothesis of the spirochaetal origin of disseminated sclerosis requires that account should be taken of spontaneous infection of the rabbit with *Spirochaeta cuniculi*. This organism, which bears many resemblances to *Treponema pallidum*, has been studied by Levaditi, Marie and Isaicu (113) and by Warthin, Buffington and Wanstrom (208). It differs from the *Treponema pallidum* in that it is a cutaneous infection which rarely becomes generalized, though Klarenbeek (98) states that generalization may occur.

Criticism of the alleged transmission of disseminated sclerosis to animals. It must be confessed that all reported experimental work claiming to demonstrate the transmission of disseminated sclerosis to animals is open to serious criticism. It is impossible here to discuss each investigation in detail, but the following criticisms are of general applicability.

. The symptoms in animals which have followed the inoculation of material from cases of disseminated sclerosis have individually borne some resemblance to the symptoms of the disease in man, but in most instances the development of the symptoms in inoculated animals has been much more acute, and often rapidly fatal. Paralysis and death have frequently been reported to occur in a few days after inoculation. A notable exception is the monkey inoculated by Steiner, and which developed symptoms eleven months later. It is, of course, not impossible that animals should be much more susceptible than man to the infective agent of disseminated sclerosis. But it is unlikely that a disease would run a markedly different course in man and animals. In spite of the high susceptibility of the guinea-pig to human tuberculosis, guinea-pigs infected with tuberculosis do not die in a few days ; and the course of the disease, though rapid, is typical. If, on the other hand, animals are so susceptible to disseminated sclerosis that it may prove fatal in a few days, it is difficult to understand why so many investigators should have failed altogether to transmit it experimentally.

It is regrettable that the majority of alleged successful transmissions of disseminated sclerosis to animals are unsupported by histological examination of the nervous system of the inoculated animals. Such histological examinations as have been made have not, with possibly one exception, revealed the pathological features of disseminated sclerosis. Gye's view that the histological changes in his animals were identical with those of human disseminated sclerosis is rejected by Birley and Dudgeon and by the present writer. The histological changes observed by Adams, Blacklock, Dunlop and Scott (3) were not similar to those of disseminated sclerosis ; but in character and distribution strongly resembled those produced by the *Encephalitozoon cuniculi*. Steiner's monkey

alone appears to have presented a pathological picture resembling disseminated sclerosis.

Control experiments are almost entirely lacking in the reported experimental work on disseminated sclerosis, and in no instance has the number of control animals inoculated been adequate. The best controlled work appears to be that of Adams, Blacklock, Dunlop and Scott, who inoculated 42 animals with material from cases of disseminated sclerosis and 7 animals with control material. They obtained positive results in 14 out of the 42 animals of the former group. In the latter all were negative. So small a number of controls is clearly inadequate when positive results were obtained in only one-third of the inoculated animals.

In the absence of adequate controls none of the experimental work on disseminated sclerosis can withstand the criticism that the symptoms induced in inoculated animals may have been due to the lighting up of a pre-existing latent infection. In view of the wide distribution among animals of such infections as *Encephalitozoon cuniculi*, such an explanation may well be the right one.

The same objection invalidates the alleged transmission of the disease by passage from one animal to another.

Criticism of the spirochaetal theory. The evidence that disseminated sclerosis is due to a spirochaetal infection is equally inconclusive.

There is considerable variation in the appearance of the spirochaetes described by various authors. Thus Kuhn and Steiner's spirochaete was very fine and delicate, resembling the spirochaete of spirochaetal jaundice. Kalberlah and Adams, Blacklock, Dunlop and Scott, on the other hand, describe a spirochaete thicker than *Treponema pallidum*.

Although spirochaetes in general are not difficult to cultivate upon appropriate media, all attempts to culture the spirochaete of disseminated sclerosis have failed, even when made by observers who claim to have seen the organism. The negative experiments of Noguchi and Birley and Dudgeon must carry considerable weight.

Since the spirochaete has never been cultivated it has not been possible to attempt to reproduce the disease in animals by inoculation with the isolated organism. The nearest approach to such an experiment was the observation of Marinesco that spirochaete-containing cerebrospinal fluid obtained from inoculated rabbits produced no ill effects when injected into other rabbits.

Though the demonstration of spirochaete-like bodies in the cerebrospinal fluid of patients with disseminated sclerosis and in the cerebrospinal fluid and tissues of inoculated animals is unquestioned, there are several objections to accepting these bodies as spirochaetes. As is the case with the rest of the experimental work on disseminated sclerosis, control experiments are almost completely absent. One such investigation, however, appears to be of the greatest significance. Adams, Blacklock and M'Cluskie (5), two of whom had previously presented evidence for the existence of spirochaetes in inoculated

animals, demonstrated the presence of spirochaete-like bodies in the cerebro-spinal fluid obtained from the lateral ventricles of normal monkeys, rabbits, and guinea-pigs. These structures could be stained with Giemsa's solution and by Becker and Fontana's methods. All attempts to cultivate them failed. In view of this demonstration of spirochaete-like bodies in the cerebrospinal fluid of normal animals of different species and the absence of control experiments, no pathological significance can be attached to similar bodies when found in inoculated animals. Noguchi draws attention to the ease with which morpho-logical elements in blood and emulsions of organs may be mistaken for spiro-chaetes and concludes: 'It is of course unlikely that Kuhn and Steiner interpreted these filaments as delicate spirochaetes of the Leptospira group, yet the description of their spirochaete strikingly suggests the forms just referred to.'

It appears unlikely that *Spirochaeta cunicula* has been a source of error since it is agreed that this organism does not become generalized.

Even if, in spite of the objections put forward, the bodies described be accepted as spirochaetes there is still no evidence that they are the aetiological agents of disseminated sclerosis or that they have ever reproduced this disease in animals. Fejer (56) claims to have demonstrated Kuhn and Steiner's spiro-chaetes in control rabbits and guinea-pigs and in a Berkefeld filtrate of the contents of the caecum of these animals. He believes that they are normal in-habitants of the intestine which appear in the blood-stream at death.

The presence of spirochaetes in the brain in disseminated sclerosis has been reported by a few workers. Schuster's case must be discarded on account of the positive Wassermann reaction in the blood and spinal fluid. Siemerling, Buscher, and Speer observed spirochaetes only in material examined by dark-ground illumination. The possible fallacies of this method have been stressed by Noguchi, and the workers quoted made no control observations. Jensen and Schroeder's 'fibrilles spiralées' in the nuclei of cells of the spinal cord cannot from this description alone be accepted as spirochaetes. Steiner's un-controlled histological study of one case requires further confirmation, and his identification of silver-staining debris in the nervous system with degeneration products of spirochaetes is difficult to accept without further evidence. It cannot be said that the presence of spirochaetes in the brain in cases of dis-seminated sclerosis has been established.

Evidence in favour of the Spherula insularis of Chevassut. It is premature to reach a conclusion concerning the claim of Chevassut and her collaborators that the *Spherula insularis* is the causal organism of disseminated sclerosis. She presents strong evidence that this body is present in cultures made from the cerebrospinal fluid in this disease, and absent in controls, but the evidence that it is the causal organism is at present inconclusive. Possibly on account of technical difficulties, it has not yet been demonstrated in the fluid itself, nor in the nervous tissues. In spite of vigorous inoculations of monkeys, five out of seven animals remained unaffected, and the histological changes in the other two animals cannot be claimed as those of disseminated sclerosis.

Further investigations are needed before Chevassut's contention can be regarded as proved.

Whether or not the bodies described prove to be the causal organism, their existence, if confirmed, provides a diagnostic test of great value, since they are stated to be demonstrable in 93 per cent. of cases and to be pathognomonic of the disease. Their presence or absence in the spinal fluid in neuromyelitis optica and other forms of encephalitis associated with demyelinization may throw light upon the relationship of these diseases to disseminated sclerosis.

There is, therefore, no satisfactory evidence that disseminated sclerosis has been transmitted to animals. Steiner's monkey alone exhibited both a clinical and a histological picture resembling the disease in man, but little stress can be laid upon one isolated observation. It should, however, encourage further attempts to inoculate monkeys. In spite of a considerable number of observations purporting to establish a relationship between disseminated sclerosis and a spirochaetal infection, this cannot be regarded as either proved or probable. Chevassut's recent claim that the disease is due to a filterable virus awaits confirmation.

VI. *Symptomatology.*

There are few diseases which raise such difficulties of diagnosis as disseminated sclerosis. The 'classical' clinical picture with which Charcot familiarized us, though highly distinctive, is now recognized as occurring in only 10 to 12 per cent. of cases. In the remainder the manifestations of the disease assume the most varied forms. Its onset may be acute, subacute, or chronic, its course remittent or steadily progressive. Evidence of multiple foci may be present from the outset, or the physical signs may, even for years, point only to a single lesion. Whichever be the case there are few regions of the nervous system, from the optic nerves to the conus medullaris, which may not be involved. It is convenient and helpful therefore to consider the symptomatology of disseminated sclerosis from three aspects : (1) its clinical course, that is, its mode of onset, development, duration, and termination, (2) the significance and frequency of individual symptoms, and (3) 'symptom-groups' or clinical varieties arising from the predominant involvement of a particular region. Such clinical varieties, it must be emphasized, are to some extent artificial abstractions which are not sharply to be distinguished from each other. Nevertheless their recognition has the same practical justification as the distinction of Parkinsonism, for example, as a clinical variety of epidemic encephalitis.

I. *Clinical Course.* (i) *Mode of onset.* The sudden onset of symptoms in disseminated sclerosis is well recognized. The modern tendency has been to emphasize the frequency with which the onset is insidious (Marquézy (124), Guillain (77), Souques (185), André Thomas (7), Birley and Dudgeon (25)). Souques found that the onset was insidious and slow in 73 per cent. of cases, Birley and Dudgeon in 45 per cent. André Thomas considers that it is often

earlier than first appears and may date from the age of twelve. Guillain describes paraesthesiae, transitory ocular troubles and fatiguability of gait as the earliest symptoms. Bohmig (26) has analysed the histories of 163 cases and found the following frequency of early symptoms: disturbances of gait in 64 per cent., paraesthesiae in 26 per cent., sphincter disturbances in 24 per cent., giddiness in 19 per cent., diplopia in 18 per cent., pain and weakness of the back in 13 per cent., disturbances of speech in 6 per cent., abnormalities in the upper extremities in 4 per cent., and facial weakness in 1 per cent.

Marquézy makes a useful distinction between 'monosymptomatic' and 'oligosymptomatic' onset. He classifies the early symptoms in his 41 cases as follows:

' 1. *Monosymptomatic onset* (16 cases). Fatiguability of lower limbs 6 times, paraesthesiae 4 times, amblyopia 5 times, pareses twice.

2. *Oligosymptomatic onset* (25 cases). Paraesthesiae 15 times, pareses 10 times, fatiguability of the lower limbs 9 times, staggering gait 7 times, amblyopia 7 times, speech disturbances 5 times, diplopia 4 times, intention tremor 4 times, giddiness 3 times, urinary disturbances 3 times, hemiplegia once.' There is thus considerable agreement between Bohmig and Marquézy as to the relative frequency of the early symptoms, though Bohmig makes no mention of amblyopia, and neither alludes to the general symptoms of infection, such as pyrexia, which may occur.

Great diagnostic stress is rightly laid upon the tendency of the disease to relapses and remissions. Birley and Dudgeon found that in 85·7 per cent. of their patients the disease had run a discontinuous course, but its development had been apparently steadily progressive in the remaining 14·3 per cent. The rare occurrence of acute and rapidly fatal cases is discussed in another section.

(ii) *Age of onset.* The occurrence of disseminated sclerosis in children has been reported not infrequently in the past, and it is perhaps significant that such reports have been much less common of recent years. The subject has been recently reviewed by Wechsler (209), who concludes that in the majority of cases the diagnosis was incorrect. Many diseases which in some ways resemble disseminated sclerosis are now recognized, and in the past confusion has probably arisen with Schilder's disease, neuromyelitis optica, acute disseminated encephalo-myelitis, hepato-lenticular degeneration, tuberose sclerosis, and other conditions. ' Nevertheless,' as Wechsler says, ' a few authentic cases remain,' but the occurrence of disseminated sclerosis before the age of ten is, to judge from the literature, probably even rarer than its familial incidence.

The following table sets forth the age distribution in decades of 1,003 patients with disseminated sclerosis, composing the series of Wechsler (209), Klausner (99), Marburg (120), Müller (137), Berger (20), Jelliffe, Morawitz, and Bing and Reese (24):

Age of patient	11–20	21–30	31–40	41–50	51–60	Over 60
Percentage of total	12·0	35·5	32·4	13·3	6·1	1·0

It will be seen that the incidence in the third and fourth decades is approximately equal, and that 67·9 per cent. of patients are between 20 and 40.

(iii) *Duration*. The duration of the disease is notoriously variable, and ranges from a few months to twenty or thirty years. Bramwell (33) found the average duration in thirty-six fatal cases to be seven years and nine months. Birley and Dudgeon found the average duration before examination to be four years. Wechsler's figures show that only 5 per cent. out of 192 patients gave a history of more than five years. The extremes in the reviewer's experience are represented by a patient who died within three months of his first recognized symptoms and one who is still able to carry on his occupation of serving behind a counter more than twenty-six years after the onset of his illness. The latter's history well illustrates the relapsing character of the disease. In 1903 he had an attack of numbness of the left arm and leg which disappeared in five weeks. In 1906 he had ' optic neuritis '; in 1914 weakness of the legs with numbness of the left; in 1917 precipitancy of micturition; and in 1928 he began once again to lose power in the left leg. A very large degree of recovery occurred after each recrudescence. Fleischer (62) has pointed out that a number of years, up to fourteen, may elapse between an attack of retrobulbar neuritis and the development of further symptoms of disseminated sclerosis. Long intervals, up to twenty years, between the appearance of symptoms have been described by many writers. Curschmann describes such cases as a ' benign form '.

(iv) *Termination*. The ordinary termination of disseminated sclerosis is too familiar to need much description. Increasing paralysis and ataxia cause the patient to become bedridden, and spastic paraplegia or pseudobulbar palsy leads to urinary, cutaneous, or pulmonary infections as terminal complications.

Rare, but of considerable importance, is the terminal occurrence of what appears to be an extremely acute exacerbation of the disease. The termination of disseminated sclerosis by an ' acute myelitis ' was described many years ago by Vulpian and Babinski. Marquézy observed this termination in four of his forty-one cases, but pathological examination apparently revealed no correspondingly acute changes in the spinal cord. Claude and Alajouanine (44) and Sézary and Jumentié (174), however, have described similar endings with the pathological picture of an acute myelitis characterized by marked perivascular infiltration and demyelinization.

(v) *The effects of lumbar puncture on the course of the disease*. In the case described by Claude and Alajouanine, and in a similar case of Guillain and Marquézy, the terminal myelitis developed shortly after lumbar puncture. Bohmig has investigated the effects of this diagnostic operation upon patients suffering from disseminated sclerosis. He did not find any severe sequels such as those just mentioned, but in 38 per cent. of cases new symptoms appeared for the first time within two or three weeks after lumbar puncture. In eleven cases these symptoms involved the lower limbs. Paresis of the external rectus occurred four times and facial paresis twice.

II. *Individual symptoms*. (i) *Relative frequency of symptoms*. Many of

the symptoms of disseminated sclerosis are so well known that they call for no
detailed discussion.   We shall, therefore, first consider the relative frequency of
all the common symptoms and devote special attention only to those which
present features of special interest or diagnostic difficulty.   The following
table shows the relative frequency with which individual symptoms were found
in four groups of cases, those of Birley and Dudgeon, Sachs and Friedman (164),
Marquézy, and Bohmig, drawn from England, the United States, France, and
Germany respectively:

	Birley and Dudgeon.	Sachs and Friedman.	Marquézy.	Bohmig.
Mental symptoms	—	15·6	—	4·7
Lack of emotional control	51·4	17	—	—
Scanning or ataxic speech	28·6	36	21	16·3
Pallor of optic disks	57·6	32·6	54	33
Nystagmus	74·3	70	70	56·2
Diplopia	34·3	29	34	—
Vertigo	51·4	8·25	39	—
Intention tremor	42·6	55·3	34	41·5
Signs of cerebellar defect	42·6	—	50	—
Spastic weakness of lower limbs	45·7	81·7	—	77·6
Ataxic or spastic ataxic gait	51·4	43·2	83	—
Absent abdominal reflexes	77·1	—	68	64·1
Extensor plantar reflexes	91·4	78·3	99	—
Sphincter disturbances	71·4	40	40	26
Paraesthesiae	82·6	30	75	13·2
Objective sensory loss				
Postural sensibility	65·7	17	—	—
Vibration sensibility	60·8	—	32	—
Cutaneous sensibility	31·4	16·3	—	—

Table showing the relative frequency of different symptoms expressed as the percentage
of patients in whom they were found by different observers.

Many factors influence the frequency with which the same symptom is
recorded by different observers, and it is noteworthy that differences in the
figures recorded in the above table are most evident in respect of symptoms the
recognition of which depends most upon the personal interpretation of patients
and physicians; for example, sensory symptoms. There is much agreement con-
cerning the frequency of signs which are objective and easily demonstrated.
Also, differences in the stage of the disease at which the patients were examined
will influence the frequency with which individual symptoms are present.
Birley and Dudgeon's figures appear the most worthy of acceptance.

(ii) *Mental symptoms.*   Until recently the mental symptomatology of dis-
seminated sclerosis has received very inadequate attention.   Numerous isolated
cases have been reported in which psychoses resembling general paralysis or
schizophrenia have been attributed to disseminated sclerosis, but, as Guillain
points out, these publications were mostly made before the days of diagnostic
lumbar puncture and the Wassermann reaction.   As recently as 1921 the
American Association for Research in Nervous and Mental Diseases reached the
conclusion 'that there is no particular psychic disorder characteristic of this
disease'.   In striking contrast with this view are the conclusions of Wilson and
Cottrell (212), who found that the 'vast majority' of 100 patients with dis-
seminated sclerosis showed certain well-defined changes in prevailing emotional

disposition, emotional expression and control, and sense of physical well-being. While the majority showed an increased sense of mental and physical well-being —called by Wilson and Cottrell 'euphoria' and 'eutonia sclerotica'—some were depressed and pessimistic. Associated with euphoria and eutonia there was often a persistent optimism as to the prognosis, described as 'spes sclerotica' by analogy with spes phthisica. Wilson and Cottrell found that intellectual disorders were minimal and negligible. They attribute the disorders of feeling-tone to invasion of the palaeothalamus by periventricular sclerosis, and consider that they may perhaps be toxic in origin. Loss of emotional control is to be differentiated from the affective disorders, with which it is not necessarily associated.

Wilson and Cottrell's valuable analysis of the mental symptoms of disseminated sclerosis omits, however, one of importance, namely, the predisposition to hysteria which clinical experience has long associated with this disease. Hysterical symptoms, such as pareses and ataxia, seem to occur more often in association with disseminated sclerosis than with any other organic disease of the nervous system. In two of the reviewer's patients, both male, hysterical fugue occurred as an early symptom. While allowance must be made for the tendency of hysterical symptoms to develop as reactions to organic disease, this would not explain their special association with disseminated sclerosis. It seems not unlikely that this disease, for unknown anatomo-pathological reasons, predisposes to the state of mental dissociation which psychologically underlies the production of hysterical symptoms.

(iii) *Convulsions.* The occurrence of convulsions as a symptom of disseminated sclerosis has been reported from time to time. Wilson and MacBride (213) in 1925 were able to find eight cases in the literature and added seven more from their own experience. These authors describe Jacksonian attacks, which may or may not be followed by hemiparesis; generalized epileptic attacks; one doubtful case of petit mal, and one case of epilepsia partialis continua. Nattrass (138) shortly afterwards reported three additional cases. Epilepsy is admittedly an infrequent symptom of disseminated sclerosis, but its occurrence may be misleading unless such a cause is borne in mind. Riddoch and Brain (159) have reported a case in which the fits led to an erroneous diagnosis of intracranial tumour. This patient, 'after suffering for several years from occasional generalized epileptiform convulsions, developed a progressive weakness of the right lower limb with increased tendon reflexes and an extensor plantar response on the right side, and some loss of postural sensibility in the toes of the right foot. These were the only signs of nervous disease, but autopsy showed the case to be one of disseminated sclerosis, with a particularly large plaque in the upper part of the precentral and postcentral convolutions on the left side'. Rönne and Wimmer (161) have described Jacksonian convulsions in a case in which the disease proved fatal in three months.

(iv) *Ocular symptoms.* (a) *Disturbances of the ocular movements.* Disturbances of the ocular movements need little discussion. Nystagmus is present

in some 70 per cent. of cases. Paresis of single ocular muscles is not very common (6 per cent. of cases, Marquézy) and usually transitory. Diplopia is commoner (30–34 per cent. of cases). Paresis of conjugate ocular movement is comparatively rare. Antoni (10) describes three cases showing an unusual disturbance of lateral conjugate movement, which he ascribes to bilateral lesions of the posterior longitudinal bundles. On lateral deviation there is nystagmus of the abducting eye and weak adduction of the other, with a resulting divergent squint and diplopia. The syndrome is bilateral, but normal adduction occurs during convergence.

Pupillary disturbances are insignificant. It is generally agreed that the Argyll-Robertson pupil is extremely rare. Guillain, and Lagrange and Marquézy (105) lay some stress on hippus. Veraguth describes total ophthalamoplegia interna.

(b) *Retrobulbar neuritis.* The pathology of the lesions in the optic nerves, chiasma, and tracts in disseminated sclerosis has already been considered. The macular fibres are predominantly damaged, partly owing to the frequent involvement of the central portion of the optic nerve, partly possibly owing to the special susceptibility to injury of these, the most highly evolved elements in the visual afferent system. As is the case with the lesions of disseminated sclerosis elsewhere the pathological process may be so insidious that no visual disturbance is noticed by the patient. In more acute cases transitory attacks of amblyopia may be produced, and in the most acute cases of all the symptoms are those of acute retrobulbar neuritis. The ophthalmoscopic appearances depend upon the severity, stage of development, and situation of the lesion. In acute retrobulbar neuritis, if the lesion is situated some distance behind the disk, the latter may appear normal, since the resulting atrophy takes some weeks to develop. When the lesion is near the disk, hyperaemia of the papilla or actual papillitis may be present (Fleischer (62), Velter (205), Bollack (27), Holden (89)), but the oedema of the disk is never great. The late ophthalmoscopic results of the optic nerve lesions, whether insidious or acute, is an atrophy of the nerve fibres, especially of the macular bundle, visible as pallor of the optic disk. Since the macular fibres run in the temporal half of the disk this is the region most affected, especially its inferior third, but in severe cases the whole disk may be pale.

The visual field defects produced by disseminated sclerosis have received much attention. Central scotoma associated with acute retrobulbar neuritis is too familiar to require description. Klingmann (100) in 1910 investigated the visual fields of twelve cases of disseminated sclerosis. In eleven he found an irregular contraction of the visual fields, especially for colours. Dyschromatopsia was present in four. Eleven showed multiple small paracentral scotomas, usually in the temporal halves and usually bilateral, and one a large unilateral scotoma in the temporal half. Marquézy has studied the visual fields in twenty-four cases. In six he found a central scotoma for red and green, in three a peripheral constriction of the fields for white and for colours. Twice Marquézy observed a

central scotoma for green on one side associated with a concentric constriction for green in the opposite field. Marquézy has not observed the small paracentral scotomas described by Klingmann. Holden describes central and paracentral scotomas and peripheral constriction of the fields. Neither Marquézy nor Holden lay stress upon the last-named symptom, which may well be the result of suggestion. Complete blindness and even severe visual loss are rare.

Impairment of vision may occur very early. Gordon (70) found that retrobulbar neuritis was the first symptom in 5 out of 56 cases of disseminated sclerosis, and Lagrange and Marquézy accept this frequency as approximately correct. It is also widely recognized that it may precede other symptoms of the disease by many years, even as many as fourteen (Fleischer). These facts render the diagnosis and prognosis of retrobulbar neuritis a question of great importance. Several investigators have followed cases of acute retrobulbar neuritis with a view to determining what proportion of them later develop disseminated sclerosis. Fleischer found that this occurred in 21 out of 30 cases of acute retrobulbar neuritis and in 5 out of 12 cases of acute optic neuritis. In 6 cases no further symptoms appeared until from four to fourteen years after the ocular onset. Marburg (121) found that 14 out of 24 cases of retrobulbar neuritis subsequently developed disseminated sclerosis. Weill (210) investigated neurologically 22 out of 25 cases of retrobulbar neuritis. Twelve already showed signs of disseminated sclerosis, 5 subsequently developed the disease, and the rest passed out of observation. On the other hand, Lenoir (111) takes a favourable view of the prognosis of retrobulbar neuritis, having followed 11 cases ' for some time ' and found no evidence that disseminated sclerosis had developed in any of them. Friedinger (67) similarly followed 26 cases for five years and found the disease in 3 only.

What prognostic considerations should influence the practitioner dealing with a case of acute retrobulbar neuritis ? It is not difficult to exclude alcohol and tobacco as causes. Syphilis, stressed by French writers, though apparently an infrequent cause in this country, can be excluded by serological tests. Thorough investigation of the nasal sinuses will eliminate these as sources of infection, though the current tendency is to minimize the importance of nasal sinusitis in the aetiology of retrobulbar neuritis (Lagrange and Marquézy (105), Bollack (27), Weill (210)). It is clear from the figures quoted above that every case of retrobulbar neuritis for which no other cause can be found should be regarded as a possible case of disseminated sclerosis, and should be subjected to a complete neurological examination, including if possible an examination of the cerebrospinal fluid. It must be borne in mind that the absence of further symptoms for many years does not exclude the possibility of the ultimate development of disseminated sclerosis.

(v) *Auditory and vestibular disturbances.* Auditory disturbances are rare in disseminated sclerosis, but transitory deafness has been described by O. Beck and other writers, and Bárány (13) has reported a case of deafness simulating acoustic neuroma.

Vestibular disturbances have received some attention, especially from French authors, but it is by no means certain that all symptoms which have been attributed to lesions of the vestibular tracts have really been so produced. Vertigo may justly be regarded as frequently vestibular in origin, and its frequency, especially in the early stages of the disease, has already been noted. Caloric, rotatory, and galvanic tests of vestibular excitability have been carried out by Marquézy (124), Barré and Reys (17), and Friesner (68). In the majority of cases the responses are normal, but both hyper- and hypo-excitability have been observed in a small proportion of cases. It is difficult to accept the view of Marquézy and Friesner that rhythmical nystagmus is always vestibular in origin. Dissociation of the normal responses to vestibular stimulation is, however, important evidence of a lesion involving the central vestibular connexions. Both Bárány and Friesner describe cases in which caloric labyrinthine stimulation produced vertigo and pass-pointing but not nystagmus, and Friesner in four cases has observed a difference in the rhythm of the nystagmus induced in the two eyes by the same method. In spite of these findings the 'vestibular' and 'vestibulo-pyramidal' forms of the disease (Barré and Reys) are rare, and we cannot follow these authors in giving to labyrinthine disorders the preponderating place hitherto attributed to the cerebellar disturbances in disseminated sclerosis.

(vi) *Sensory disturbances.* The variety and frequency of sensory disturbances in disseminated sclerosis has been recognized only comparatively recently.

Paraesthesiae. The frequent occurrence of paraesthesiae, especially as early symptoms, has already been noted. Birley and Dudgeon found them in 82·6 per cent. of cases, Marquézy in 75 per cent., Keschner and Malamud (97) in 63·6 per cent., Sittig (183) in twelve out of fourteen cases. Sachs and Friedman, and Bohmig gave lower figures, but the higher are probably correct. As Sittig points out, it is necessary to make special inquiry for these symptoms as the patient often omits to mention them. Sittig describes many varieties of paraesthesiae. Numbness or formication may involve one half of the body, one limb or a part of a limb, or occupy a segmental distribution, e. g. preaxial or postaxial in the upper limb. They are transient and constantly changing. Lhermitte, Lévy and Nicholas have reported two cases in which sensations resembling electric shocks radiated through the body when the patient flexed the cervical spine. The reviewer has seen a similar case. Pruritus has been observed (Guillain).

Pain. Spontaneous pains, though comparatively uncommon, are important, since if their significance is misunderstood they may be misleading. They are sometimes severe and may involve the limbs, e. g. sciatic pain, pain in the shoulders, or trunk, girdle pains. The pains are said to be 'boring' or 'neuralgic' but not lancinating. Vertebral tenderness may be present. Headache may occur.

Trigeminal pain, simulating in every respect tic douloureux, may afflict the

patient (Oppenheim, H. (144), Marburg (120), Berger (20), Guillain, Harris (82), Parker (146)).   In Oppenheim's, and one of Parker's cases, it was associated with a plaque in the pons at the site of entrance of the trigeminal nerve.   Harris has observed twenty-three cases in which trigeminal neuralgia, often bilateral, was associated with spastic paraplegia.   He considers that the majority of these were cases of disseminated sclerosis, and states that the neuralgia is unassociated with objective sensory loss and responds to alcoholic injection in the same way as tic douloureux.

Objective sensory loss.   Objective sensory loss has been found in 50 to 65 per cent. of cases in some series.   (Keschner and Malamud, Birley and Dudgeon.) The former found 'spinothalamic' sensibility slightly more frequently affected than 'posterior column' sensibility.   Most authors agree that the reverse is the case.   Birley and Dudgeon found an impairment of postural sensibility in 65·7 per cent., of appreciation of vibration in 60·8 per cent., and of cutaneous sensibility in 31·4 per cent. of their cases.   Astereognosis is uncommon and most characteristically occurs as a feature of ' the useless arm ' first described by Oppenheim, H. (144) and Cassirer (38).   This symptom complex is attributable to the development of a lesion in the lateral portion of one posterior column in the upper cervical cord, with resulting gross loss of postural sensibility and tactile discrimination in the ipsilateral upper limb which exhibits astereognosis and sensory ataxia.   Birley and Dudgeon have observed this phenomenon in the high proportion of 40 per cent. of their cases.

Keschner and Malamud draw attention to the occurrence of 'sensory levels'—that is, relative or absolute sensory loss with a well-defined upper border, segmental in character.   Such sensory levels occurred in fifteen out of their forty-two cases.   In eight of these cases the diagnosis of tumour of the spinal cord was seriously considered, and in four exploratory laminectomy was actually performed.   The reviewer has observed a case in which there was loss of all forms of sensibility below a well-defined zone of hyperalgesia in the upper dorsal region, associated with progressive paraplegia of nine months' duration. In this case also exploratory laminectomy was performed.   The diagnosis of disseminated sclerosis was established at autopsy.

(vii) *Muscular wasting.*   Localized muscular wasting due to involvement of the anterior horns of the spinal grey matter in a plaque is one of the rarest symptoms of disseminated sclerosis.   It is said to be sometimes sufficiently widespread to simulate amyotrophic lateral sclerosis (Lejonne (109)), but Guillain considers this exceptional.   Bing and Reese classify two of their 281 cases as ' amyotrophic '.   Localized wasting may involve one half of the tongue (Oppenheim), the small muscles of the hands (Fraenkel and Jakob (65)), one upper limb (Rönne and Wimmer (161)), the shoulder girdle, quadriceps, or peronei (Curschmann (47)).

(viii) *The cerebrospinal fluid.*   Examination of the cerebrospinal fluid forms an important part of the investigation of a case of disseminated sclerosis, since ' in approximately half of the fluids there are pathological changes which cannot

be overlooked' (Ayer and Foster (11)). Many papers on the subject have been published, and there appears to be general agreement as to the nature and frequency of the abnormalities found. The following summary is based mainly upon the researches of Ayer and Foster, Marquézy (124), and Souques, Blamoutier, de Massary, Lafourcade and Terris (186).

The pressure is sometimes slightly raised. The naked-eye appearances are normal. In at least half the cases the cell count is normal. More than 10 cells per c. mm. were found in 5 out of 47 counts (Souques et al.) and 11 out of 51 counts (Ayer and Foster), with maximal counts of 231 and 42 respectively. The cells are mononuclear in type. The total protein is usually just below the upper limit of normal, 40 mg. per 100 c.c. It is somewhat above normal in 15 to 20 per cent. of cases, but never very high. The Nonne-Apelt and Pandy tests for globulin occasionally yield a positive response, the former in about one-third of cases (Ayer and Foster). The Wassermann Reaction is negative.

Ayer and Foster carried out the colloidal gold test on 42 specimens obtained from 33 patients, with the following results:

So-called 'paretic' type   21 fluids in 16 patients.
So-called 'luetic' type   7 fluids in 7 patients.
Other positive reactions   3 fluids in 3 patients.
Negative reactions   11 fluids in 10 patients.

There was thus a 'paretic' curve in about half the cases, and some other abnormality in a further quarter.

The colloidal benzoin test, introduced by Guillain, has been used especially by French workers. Guillain and Marquézy obtained positive or subpositive results in seventeen out of twenty-seven cases, namely, subpositive fourteen times, positive of the syphilitic type twice, and of the paretic type once. Guillain points out the correspondence between this incidence of 63 per cent. positive or subpositive results with the results yielded by the colloidal gold test. Souques and his collaborators obtained similar results.

Ayer and Foster believe that the 'paretic' type of gold curve often indicates a progressive phase of the disease and that a negative result is more often obtained from stationary cases. Marquézy, however, doubts this. Adams, Blacklock, Dunlop and Scott have observed a diminution in the colloidal gold curve in response to treatment with salvarsan.

The *sugar* and *chlorides* of the fluids show no characteristic changes.

III. *Symptom groups.* The predominant involvement of different regions of the nervous system leads in the early stages of the disease to widely differing clinical pictures. These need be only briefly described here as their symptoms have in most cases been considered in the previous sections.

(i) *The classical form.* The classical triad of symptoms described by Charcot—nystagmus, intention tremor, and scanning speech—occurs in about 10–12 per cent. of cases only.

(ii) *The generalized form.* This is the 'common form' of Guillain. As the 'symptomreich' form of Bing and Reese it constituted 37 per cent. of their

cases. Pallor of the optic disks, nystagmus, slight intention tremor, ataxia, spasticity, and weakness of the lower limbs indicate the wide dissemination of the lesions. This form is especially common among younger patients, and as a rule is fairly rapidly progressive.

(iii) *Onset with ocular symptoms.* In this important group ocular symptoms, especially retrobulbar neuritis, may be the only manifestation of the disease for many years.

(iv) *Onset with hemiplegia.* Hemiplegia appeared in 2 per cent. of Bing and Reese's cases. Recovery is often rapid and strikingly complete.

(v) *Spinal forms.* (a) *Progressive spastic paraplegia.* Paraplegia was the predominant symptom in nearly one quarter of Bing and Reese's cases. Some cases of Erb's spastic paraplegia are due to disseminated sclerosis (Guillain). This form is common in older patients. Sensory loss is a variable concomitant.

(b) *Brown-Séquard lesions.* Lesions which predominantly involve one half of the cord are commonest in the cervical region. The posterior column may suffer severely ('useless hand' of Oppenheim).

(c) *Sacral form.* Oppenheim (143), Mendel (129), and Curschmann (47) have drawn attention to cases characterized by incontinence of urine and faeces, impotence, and anaesthesia in the region of the sacral cutaneous supply. These symptoms are attributable to a plaque in the conus medullaris.

(vi) *Cerebellar,* (vii) *vestibular,* (viii) *pontine,* and (ix) *bulbar forms* are sufficiently described by their titles.

(x) *Acute forms.* The rare occurrence of acute forms seems to be established. Their duration is frequently about three or four months. The onset is exceptionally rapid. Headache and vomiting may occur and optic neuritis may develop. Cranial nerve palsies are commoner than in more slowly progressive forms (58), (65), (85), (119), (150), (161).

VII. *Treatment.*

It is notoriously difficult to assess the value of therapeutic measures in disseminated sclerosis, and most advocates of some particular line of treatment qualify their optimism by alluding to the natural tendency of the disease to spontaneous remissions. That such a qualification is necessary seems to indicate that no mode of treatment is successful enough to achieve, at the most, a greater improvement than might have occurred spontaneously.

Concerning general measures little need be said. The great importance of rest and the avoidance of fatigue are generally recognized, but permanent confinement to bed should be deferred as long as possible. The high susceptibility of the patient to hysterical embroidery of his symptoms demands psychological insight on the part of the physician, whose encouragement and optimism are often of greater value than his pharmacological essays. The general treatment in the late stages is too familiar to need discussion here.

1. *Special therapeutic measures.* The induction of pyrexia is one of the most important methods of treatment.

(i) *Malaria treatment* is advocated by Dreyfus and Hanau (54), who treated twelve cases, eleven of which were improved. Grosz (75), however, obtained less satisfactory results. He treated forty-two cases on the same lines as for general paralysis. Eleven showed definite improvement, and eighteen were benefited to a less extent. Following the malaria treatment he administered neo-arsphenamine.

(ii) *Typhoid vaccine* has been given intravenously by a number of workers. MacBride and Carmichael (117) treated seventy cases in this way, beginning with doses of 25 millions and increasing in a course of eight or ten injections up to 400 millions. They believe that this method of treatment gives more satisfactory results than any other. Dreyfus and Hanau, after giving three to six intravenous injections of typhoid vaccine alone, administered it suspended in a solution of novarsenobillon, giving injections every three or four days until ten or twenty had been given. They found this treatment less satisfactory than malaria treatment. Schacherl (167) has employed a similar technique, giving both typhoid vaccine and N.A.B. in 10 c.c. of 10 per cent. solution of calcium chloride.

(iii) *Other pyrogenic agents* have been employed—injection of milk, phlogetan (Barré 16), sulfosin (175), and inoculation with the spirochaete of African relapsing fever (John 95)—with but doubtful results.

Grosz (74) has obtained benefit from the subcutaneous injections of vaccines which produced no general reaction. He treated twenty-six cases with polyvalent staphylococcal vaccines and twenty cases with typhoid vaccine. Eighteen of the latter also had neo-arsphenamine. He gave 10 millions as the first dose, and gave an increasing dose every two to four days up to 1 to 2,000 millions. Typhoid vaccine combined with neo-arsphenamine gave the best results, there being marked improvement in 30 per cent. of cases. Grosz considers this mode of treatment more effective than malaria treatment. MacBride and Carmichael (117) also treated two cases with subcutaneous injections of typhoid vaccine with beneficial results.

Purves-Stewart (155) has employed a vaccine prepared from the organism described by Chevassut (40) in the cerebrospinal fluid of patients with disseminated sclerosis. Cultures of this virus were killed by the addition of 0·5 per cent. carbolic acid solution, and autogenous vaccines were administered intravenously in doses ranging from 1 to 1,500 millions. Purves-Stewart claims that the administration of this vaccine may lead to clinical arrest of the disease, improvement in the colloidal gold curve and globulin reaction of the cerebrospinal fluid, and disappearance of the organism from the cerebrospinal fluid. Seventy cases have been thus treated, with the following results. Clinical arrest occurred in forty cases, while thirty were uninfluenced. Improvement in the colloidal gold and globulin reactions in the cerebrospinal fluid occurred in forty-nine cases, but in only eight cases out of the seventy did the organism disappear from the cerebrospinal fluid. Purves-Stewart describes his communication upon this subject as 'necessarily a preliminary one', and his cases have only been under

observation for two or three years. It is clearly premature to assess the value of this mode of treatment, but the fact that the organism only disappeared from the cerebrospinal fluid in eight cases out of the seventy indicates that even if Chevassut's *Spherula insularis* proves to be the causal organism of the disease there yet remain considerable difficulties in the way of therapeutic applications of her discovery.

Dumas and Foix (55) have employed the serum of non-progressive cases; Boveri (29) has administered Pettit's antipoliomyelitis serum. Laignel-Lavastine and Koressios (106, 107, 108) advocate administering the serum of rabbits which have been inoculated with the patient's red blood-cells and cerebrospinal fluid. These sera probably operate merely as foreign proteins. Purves-Stewart considers that it may be possible to employ Chevassut's organism in the production of immune sera which may possess therapeutic value.

Arsenic in the form of liquor arsenicalis has been administered orally in disseminated sclerosis for a considerable time. The intravenous administration of organic compounds of arsenic appears to have been inspired by the theory of the spirochaetal origin of the disease. *Sodium cacodylate* has been used Koster (101), but Barré doubts its utility. *Novarsenobillon* has been widely employed. In general it has been used more cautiously than in the treatment of neurosyphilis. Siemerling (178) advocates beginning with 0·075 grm. and increasing up to 0·3 grm. He administers it in 5 or 10 per cent. solution of calcium chloride or afenil. Its use in conjunction with or supplementary to vaccine and malaria treatment has already been described. *Silver-salvarsan* is said to yield better results than N.A.B. Schafgen (168) found that improvement followed treatment with the former in 68 per cent. and with the latter in 37 per cent. of cases. Sauer (166) gives doses of 0·05 to 0·15 grm. twice a week until 3 grm. have been given. Osnato (145) emphasizes the importance of persistent treatment. He continues courses of ten weekly injections for two years. Silver-salvarsan is advocated by Steiner (192), Stern-Piper (197), Sauer (166), Bertolani del Rio (21), Prados y Such (154), Adams, Blacklock, Dunlop and Scott (3), but Fleck (61), Speer (187), Simmonds (180), and Veraguth (207) are sceptical of its value.

The intravenous injection of colloidal silver is recommended by Ohnsörge and Fischer (139). They have employed electro-collargol (Heyden) in doses of 2 c.c. of 0·06 per cent. suspension, increasing to 5 c.c. Injections are given two or three times weekly until 40–50 c.c. have been given. If a general reaction follows the first injection the dose is not increased on the next occasion. Guillain (78) and Poussep (153) also recommend colloidal silver. Inunctions of silver in the form of Crede's ointment have been used by Fischer (59).

Crecelius (46) and Delius (52) have used antimony. The former has employed stibenyl, Heyden '661', and antimosan. Stibenyl was given intramuscularly and intravenously in doses of from 0·02 to 0·05 grm., two injections a week being given until 0·2 grm. had been administered in a course. The preparation Heyden '661' was employed in a dilution of 1 in 100, beginning with

a dose of 0·03 grm. and increasing up to 0·2 grm. An injection was given every four or five days, 3 to 4 grm. constituting a course. Antimosan is a preparation of which 1 c.c. contains 0·05 grm. of antimony. The maximal dose was 5 c.c. twice a week intravenously or intramuscularly, a course consisting of 4 grm. These drugs are considered by the authors to be beneficial.

'*Bayer 205*' is advocated by Kulkow (104), who has employed a 10 per cent. solution in saline, giving 5 c.c. intravenously every five or six days. After ten injections the drug is withheld for three or four weeks.

Foix, Chavany and Lévy (63) have used sodium salicylate, giving daily intravenous injections of 0·05 grm. for 20 consecutive days. Others advocate intramuscular injections of urotropin, quinine hydrochloride, and mercury (Guillain (78)), mercury inunctions combined with iodides by the mouth (Adams et al. (3)), vasodilators, e. g. pilocarpine and the nitrites (Barré (16)). Habetin has observed improvement following the intramuscular injection of 5 c.c. of a 5 per cent. solution of sodium nucleinate.

Stephenson (196) has reported improvement following the use of diathermy, one electrode being applied over the vertebral column. This is said to be advantageous when the lesions are predominantly spinal. Horwitz and Koolman (92) found that benefit resulted from deep X-ray irradiation in about onehalf the cases treated. Léri (112) has observed slight improvement after irradiation with ultra-violet rays.

The multiplication of remedies is eloquent of their inefficacy. The organic compounds of arsenic are the most popular therapeutic agents, but there is no general agreement as to their value. This fact, in contrast with the status of these drugs in the therapy of neurosyphilis, suggests that they probably have no specific action upon the cause of disseminated sclerosis. Therapeutic applications of Chevassut's observation of a virus in the cerebrospinal fluid are still in the experimental stage. The various forms of pyrexial treatment appear to be the most effective therapeutic measures at present available, but they cannot be expected to do more than retard the progress of the disease. They can accomplish nothing in advanced cases, and would seem to be indicated especially in early but apparently rapidly progressive cases. Diathermy and X-ray irradiation have perhaps some palliative action, but should be employed with caution. The cure of disseminated sclerosis awaits an increase in our knowledge of the causal organism, of the nature of immunity, and of the factors upon which depend the remarkable variations in the course of the disease.

VIII. *Relationship to other Diseases.*

One of the most obscure, but most important and interesting, problems of disseminated sclerosis is its relationship to other diseases of the nervous system characterized by perivascular demyelinization. Does an acute form of the disease occur ? How is disseminated sclerosis related to neuromyelitis optica, acute disseminated encephalo-myelitis, encephalitis periaxialis of Schilder, post-vaccinial

encephalitis and encephalitis complicating measles and other exanthemata ? In recent discussions of these questions speculation has perhaps tended to outrun discretion.   In the absence of any certain knowledge of their causes our conception of the relationships subsisting between these diseases can be based only upon the notoriously insecure foundations of clinical and pathological similarities and differences. The development of our knowledge of neurosyphilis well illustrates the unreliability and temporary character of such hypotheses. In attempting to classify the demyelinating diseases we are in a similar position to the investigator of syphilis before the discovery of the *Treponema pallidum* and the invention of the Wassermann reaction.   Nevertheless, with due recognition of the provisional character of all classifications, we may at least enquire how far current clinical and pathological distinctions appear to be justified.

1. *Neuromyelitis optica.*   The association of bilateral acute optic neuritis with acute myelitis appears to have been first described by Allbutt in 1870. The condition is a rare one, but seems to have increased in frequency recently. Beck (18) in 1927 found 70 cases reported in the literature under a variety of names—acute disseminated myelitis, diffuse myelitis with optic neuritis, neuromyelitis optique aigue (Devic), ophthalmoneuromyélite and neuroptico-myélite aigue. The age of the patients ranged from twelve to sixty. Beck found that in 36 of 70 reported cases myelitis preceded the ocular symptoms ; in 18 the first symptom was the onset of blindness; in 10 cases both came on simultaneously ; and in 4 the optic neuritis was discovered only on routine ophthalmoscopic examination.   Goulden (71), however, states that the optic neuritis appears first in four-fifths of the cases. Usually one eye is first affected, to be followed by the other at some time varying from a few hours to several weeks. Rarely the onset of the myelitis intervenes between the affection of the two eyes. The ocular lesion may be a true optic neuritis or a retrobulbar neuritis.   Blindness may be complete or almost so ; or there may be bilateral central scotomas, or homonymous field defects (Holden (89)).   The acute myelitis presents the usual clinical features, and not uncommonly involves the cervical region of the cord, leading to quadriplegia. The mortality rate is about 50 per cent. (Goulden). The most remarkable feature of the condition is the striking degree of recovery that may occur. Vision may be largely restored and so may the functions of the spinal cord. Holmes (91) reports a case of apparently complete recovery in a man who at one stage of his illness was blind, quadruplegic, and breathing only by his accessory respiratory muscles. There may, however, be secondary optic atrophy with some persistent field defect, and residual sensory loss or weakness in the limbs.

Beck has recently made a thorough pathological study of a case—a girl of fifteen.   In the spinal cord there was massive demyelinization extending continuously from the seventh cervical to the twelfth thoracic segments with smaller areas of rarefaction in which the axis-cylinders were also destroyed. Marked perivascular infiltration, mainly with round cells, occurred throughout the nervous system, and not only in the demyelinated areas. Polymorphonuclear

cells were present in places. In the demyelinated areas there was a great multiplication of vessels, surrounded by many compound granular cells, and also of neuroglial cells, though with little if any formation of new neuroglial fibres. The optic nerves and chiasma also showed massive demyelinization going on to cavitation and infiltration with round cells and polymorphonuclear cells.

Beck considered that his case was clinically unlike disseminated sclerosis, and differed from that condition pathologically in respect of the presence of (1) cavitation, (2) infiltration with polymorphonuclear leucocytes, (3) massive and continuous demyelinization, and (4) perivascular round-cell infiltration throughout the nervous system.

The differentiation of neuromyelitis optica from disseminated sclerosis is based upon clinical and pathological grounds which are best considered separately. Clinically, we are asked to conceive of the former as an acute or subacute self-limited disease, with the symptoms already described, rapidly terminating in death or in more or less complete recovery, while disseminated sclerosis is to be regarded as a chronic relapsing disease with an inevitable downward course. This distinction, however, appears to be invalidated by a series of intermediate cases which are transitional between the two. The following table shows the clinical course of ten cases of myelitis associated with optic neuritis :

Author.	Case No.	Interval between Ocular and Spinal Symptoms.	Duration and Result.
Goulden (71)	—	1 week	Died 16th day
Brain (30)	—	1 week	Recovered
Holmes (90)	1	1 week	Recovered
,,	2	1–2 weeks	Died 16th day
Holden (87), (88)	4	a few days	?
,,	2	3 weeks	Died 6th week
,,	5	3 months	Traced 1 year only
,,	1	4 months	Died 5th month
,,	3	8 months	Stationary
Beck (18)	—	8 months	Died 13th month

Beck's case showed remissions and relapses, with partial recovery of vision and almost complete recovery from paraplegia during the course of the illness. It is instructive to compare this case with one reported by Lejonne and Lhermitte (110). Their patient, like Beck's, a girl of fifteen, fell ill with bilateral optic neuritis and paraplegia, from both of which she made a good recovery. After two years she again developed paraplegia, again improved, and twice subsequently relapsed, dying five years after the onset of her illness. The pathological appearances were those of disseminated sclerosis. It would seem, therefore, that all gradations of acuteness exist between the most acute cases of neuromyelitis optica and disseminated sclerosis.

Is Beck's pathological distinction of the two conditions justifiable? He bases this upon the presence in his case of neuromyelitis, of cavitation, infiltration with polymorphonuclear leucocytes, massive and continuous demyelinization, and perivascular infiltration throughout the nervous system. McAlpine (127) states that he has observed the first and the last of these features in the acuter

cases of disseminated sclerosis. Symonds (200) regarded Beck's case as one of rapidly-progressing disseminated sclerosis.

The clinical and pathological differences between neuromyelitis optica and disseminated sclerosis appear to be differences of acuteness and intensity only. Such differences, of course, may depend upon a difference in the infective agent, but in the absence of proof that this is the case there seems no justification for separating them.

2. *Acute disseminated encephalo-myelitis.* The occurrence of acute forms of encephalo-myelitis with perivascular demyelinization has long been recognized, and there has been much discussion whether they should be regarded as acute cases of disseminated encephalo-myelitis. Marburg (119) believes that the histological features of 'acute multiple sclerosis' are identical with those of recent patches in the chronic form. Pette (150, 151), Rönne and Wimmer (161), Fraenkel and Jacob (65) appear to share Marburg's view. Turnbull (203) has recently stated: 'I find it impossible to consider acute and chronic disseminated sclerosis to be other than varieties of one condition; transitions between the two and mixtures of the two have been the rule rather than the exception in my experience.' Anton and Wohlwill (9), however, consider that they are histologically distinguishable. In describing two cases of 'acute non-purulent encephalo-myelitis' they state that in the acute cases the nocuous agent not only produces in a shorter time a greater number of patches but also a more intensive, stormy, and extensive outfall of nerve-tissue and a more vigorous glial reaction. They regard the pathogenic agents in the two cases as closely allied but not identical, though as the difference is only quantitative a sharp line cannot be drawn between them. Finkelnburg (58) adopts a similar view.

Clinical distinctions are as uncertain as pathological differentiation. The majority of fatal cases of so-called acute multiple sclerosis or acute disseminated encephalitis have run a subacute rather than an acute course, terminating fatally in three or four months. Several recent writers, however, have reported under the name acute disseminated encephalo-myelitis benign cases with a marked tendency to recover (Redlich (157), Pette (150), Montzka (134), Martin (125), Brain, Hunter and Turnbull (31)). In some of these cases the onset has been much more acute than in the fatal cases of acute multiple sclerosis. It is possible that acute disseminated encephalo-myelitis is a heterogeneous group, some cases being acute examples of multiple sclerosis and others allied to post-vaccinial and measles encephalitis.

The following case, which I am able to report through the kindness of Dr. W. Langdon Brown, illustrates the difficulties of clinical differentiation. The patient, a girl of eight, at the age of four had an acute illness characterized by drowsiness, ataxia, and spastic weakness of the limbs. She made a good recovery but relapsed two years later with similar symptoms. In addition visual impairment was noted in this attack. She again recovered, but the same symptoms recurred eighteen months afterwards. On examination during the third attack she showed bilateral primary optic atrophy, nystagmus on fixation

in all directions, bilateral signs of pyramidal defect and slight ataxia, most marked in the left upper limb. In acuteness of onset and severity of general symptoms this case resembles acute disseminated encephalo-myelitis. In clinical features it recalls neuromyelitis optica, and, in its relapsing character, disseminated sclerosis. In the face of this and similar cases it is difficult to maintain a rigid distinction between the three groups.

3. *Encephalitis following vaccination and the exanthemata.* Perdrau (149) early drew attention to the pathological resemblances between postvaccinial encephalitis, acute disseminated encephalitis, and disseminated sclerosis, and suggested that they might be due to the same pathogenic agent. Study of the pathology of encephalitis following measles (Wohlwill (215), Greenfield (73)) has shown marked resemblances between this condition and post-vaccinial encephalitis. Pathologically both of these forms of encephalitis are differentiated from disseminated sclerosis by Wohlwill and Greenfield on the ground that they show demyelinization along the whole length of the affected vessels instead of along segments only. Turnbull (203), however, points out that 'the different pictures may simply represent modified reactions to a single agent, and the histological differentiation be artificial'. Pette (151) states that demyelinization along the whole length of a vessel may be observed in the acuter cases of disseminated sclerosis, the cause of which he regards as closely related to that of encephalitis following vaccination and measles.

In the absence of knowledge of the cause of these diseases such speculations must be received with caution. We do not at present know whether postvaccinial and measles encephalitis are due to the virus of vaccinia and measles or to some other neurotropic virus or viruses. In spite of their pathological similarities their symptomatology and prognosis are different. Ford's (64) recent review of measles encephalitis reveals that its mortality rate is much lower and its liability to sequels much higher than is the case with postvaccinial encephalitis. Both again are clinically distinguishable from acute disseminated sclerosis. If, however, all three are due to the same cause, the manifestations of this pathogenic agent may well be modified by the preceding exanthem. Only its isolation is likely to settle the question.

4. *Encephalitis periaxialis diffusa.* Yet another group of conditions characterized by demyelinization claims consideration in relation to disseminated sclerosis. This group includes encephalitis periaxialis diffusa of Schilder (169) and such allied disorders as aplasia axialis extracorticalis congenita of Merzbacher (131), the interlobar symmetrical sclerosis of Marie and Foix (122), the new familial form of infantile diffuse sclerosis of Krabbe (102), the encephalomyelomalacia chronica diffusa of Hermel, the encephaloleukopathia scleroticans progressiva of Flatau (60), the microcephaly and diffuse sclerosis of Freeman, and the progressive degenerative subcortical encephalopathy of Globus and Strauss (69). In these conditions there is widespread demyelinization and glial overgrowth predominantly in the white matter of the hemispheres, with adventitial infiltration with compound granular cells, and, to a variable extent,

with lymphocytes. According to Greenfield (72) the demyelinization is perivascular in its early stages in Schilder's disease.

The cause of this group of disorders is unknown, and even their pathological nature is uncertain. Schilder regarded his cases as infective in origin; Globus and Strauss consider theirs degenerative. Steiner (192) points out that the pathological picture in diffuse sclerosis varies according to the duration of the disease at death. In the more acute cases perivascular lymphocytic infiltration is very marked, a point which he considers in favour of their near relationship to disseminated sclerosis. Here, again, we may well be dealing with a heterogeneous group of disorders. The familial occurrence of some of them suggests that an endogenous cause may sometimes be an aetiological factor.

Conclusions concerning the relationships of disseminated sclerosis. It is probable that the conception of disseminated sclerosis as a chronic and progressive disease is biologically artificial. The recognition of this does not diminish its clinical value as indicating to the clinician the probable course of the disease with which he is dealing. Disseminated sclerosis remains a clinical entity. Biologically, however, it seems to merge into more acute disorders, such as neuromyelitis optica and some forms of acute disseminated encephalitis. Its relationship with post-vaccinial encephalitis, measles encephalitis, encephalitis periaxialis diffusa and diffuse sclerosis is more questionable. Clinical and pathological distinctions cannot be accepted as necessarily incompatible with aetiological identity. Pette points out that the experimental infection of animals with neurotropic viruses reveals wide variations in the diffuseness and intensity of the reaction to the same infective agent. He suggests that epidemiology and immunology will throw light upon these problems. Variations in dosage and virulence of the infective agent and in the immunity of the host may possibly account for the wide range of reactions which we regard clinically as different diseases. Such hypotheses are not of merely academic interest, but of great practical importance. To accept the evidence that neuromyelitis optica and disseminated sclerosis are probably due to the same pathogenic agent is to admit that recovery from this infection may occur. Does recovery in the former disorder depend upon a dosage of the virus which, if not immediately fatal, is sufficiently large to confer a permanent immunity? What factors are responsible for the great variability of the course of disseminated sclerosis? Does recovery from this condition ever occur? If a remission may last for twenty-four years, why not for fifty-four (6)? Does the remarkable degree of recovery possible in neuromyelitis optica and post-vaccinial encephalitis indicate that the processes which end in demyelinization are at certain stages reversible? Is such a reversibility the explanation of the high degree of recovery from the effects of a single lesion in disseminated sclerosis? These possibilities suggest the hope that the cardinal feature of disseminated sclerosis, its relapsing tendency, may, when its cause is fully understood, provide a clue to the problem of immunity and so lead to the cure of the disease.

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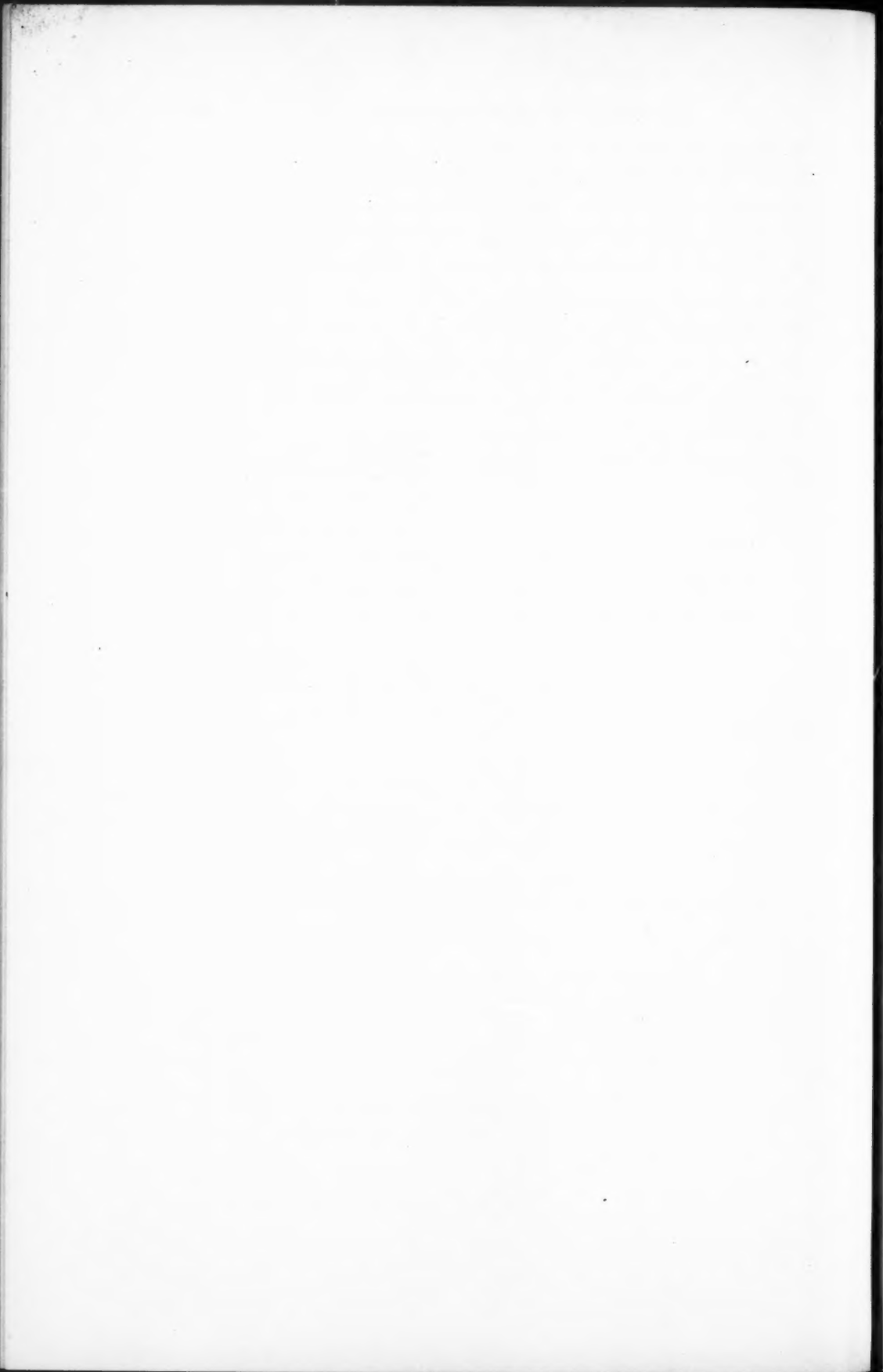
ACIDOSIS AND DEBILITY [1]

A CONTRIBUTION TO THE STUDY OF THE STATE OF THE 'SOIL' DISPOSING TO DISEASE

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IT is generally agreed that a pre-existing state of subnormal health, in popular language often called 'being run down', frequently precedes, and also disposes to, actual disease. The cause or causes of this state are often unknown, but there can be little doubt that living under unhygienic conditions, and generally unfavourable circumstances, are important contributory factors. Faulty diet, insufficient sleep, overcrowding, lack of exercise, and worry may all at times play a part in the production of this state, though it is often impossible to assess the relative importance of any one of them in a given case. But, whatever the cause, there can be no doubt as to the enormous importance of the condition itself, both because of the part it plays in the disposition to disease, constituting, in fact, the 'soil' in which disease flourishes, and because of the frequency with which it occurs, particularly amongst the so-called 'hospital classes'. It is therefore surprising that this borderland state between health and disease has not received more attention, either at the hands of physicians or research workers.

The object of this paper is to put forward and to discuss certain bio-chemical and clinical observations concerning this state, which we believe to be of considerable importance. These observations arose in the first instance out of an investigation into the disposing causes of various types of nephritis, a disease which, as pointed out elsewhere (1), is most likely to supervene where, from any cause—infection, exposure, chill, or starvation—a condition of acidosis is already induced. It became obvious, however, that the subject was of much wider significance, and the scope of the inquiry was extended to a study of ' debility ' in general—the subject of this paper.

In brief, the thesis is this: Subnormal health, or debility, is frequently associated with varying degrees of 'acidosis', a condition which, in turn, is often accompanied by, if it does not cause, other chemical and physical changes in the organism, especially those relating to alterations in the water content of the body. 'Acidosis' is herein defined as a reduction in the bicarbonate content of the blood plasma, however this may be produced; and 'alkalosis' as an

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increase above normal in this substance. It must be emphasized that this definition does not necessarily imply any change in the reaction, or pH, of the blood, a condition best described by the terms 'acidaemia' and 'alkalaemia'. Such may or may not be present. In this investigation the pH was not measured. It is also necessary to point out that, in the cases under consideration, the 'acidosis' described was found not to be due to an associated 'ketosis' or 'acetonaemia'.

It is proposed to describe first the variations in the plasma bicarbonate found in several groups of normal persons, then to contrast these with similar observations in debilitated subjects, and finally to discuss briefly in what manner these variations appear to be related to certain other changes in the body.

Although in the present investigation variations in the plasma $NaHCO_3$, NaCl, and water content of the body have been specially considered, it is important to remember that, when these show considerable departure from the normal, it is almost certain that many other equally important chemical and physical disturbances also occur—such, for example, as alterations in reaction, osmotic pressure, and electrical charges. It must be borne in mind, therefore, that in this paper an exceedingly complex problem has been approached from one aspect only.

Methods.

Blood was collected under paraffin from a vein at the elbow, into oxalated centrifuge tubes, without undue compression of the arm. The plasma bicarbonate was estimated by the method of van Slyke, Stillman and Cullen (2). Titration was carried to a constant endpoint of pH = 7·4. Phenol red was used as an indicator. The results are expressed as molar concentration of $NaHCO_3$.

(A molar solution contains a molecular weight of the solute in a litre. A molar solution of $NaHCO_3$ contains 84 grm. $NaHCO_3$ per litre, or 8·4 grm. per 100 c.c. To convert molar concentration of $NaHCO_3$ into terms of grammes per 100 c.c. it is therefore necessary to multiply by 8·4; e.g.)

(0·030 molar = 0·25 grm. per 100 c.c. = $NaHCO_3$.)

The plasma chlorides were estimated by the method of Claudius (3), the result being expressed as grammes NaCl per 100 c.c. With a few exceptions, the samples were collected two hours after the last meal, and the estimations were carried out within twelve hours. It has been found by experiment that in plasma separated from the cells the chloride content does not change in this time. It has also been shown previously (5) that, with the technique used, the plasma $NaHCO_3$ does not undergo significant changes in this period. All readings are the mean of at least two, often of three, estimations.

Presentation of Results.

In cases of debility, gross departures from the accepted standards of health, as revealed by ordinary clinical and laboratory tests, are not encountered, and likewise well-marked biochemical variations from the normal are not to be expected. As both the clinical and the accompanying biochemical changes in

debility shade off almost imperceptibly into the normal, it was decided to express the results of the bicarbonate estimations in the form of frequency curves. From these it will be seen that variations from the normal, which in a few cases would be entirely without significance, become of some importance when found to constitute, on a curve, an average shift in this or that direction, especially when the values obtained represent the results of estimations in a comparatively large number of cases in each of the groups studied. Further, these results have been submitted to statistical analysis to insure that correct sampling in each group has been obtained.

Selection of Cases.

The following groups of cases were investigated:

(a) Normal adult males . . . . . . 86 subjects
(b) Normal adult females (intermenstrual) . . 31 ,,
(c) Normal adult females (menstrual) . . . 31 ,,
(d) Normal pregnant females . . . . . 68 ,,
(e) Normal children . . . . . . 38 ,,
(f) Debilitated adult females . . . . . 72 ,,
(g) Debilitated children . . . . . . 68 ,,

The normal adult males were all healthy medical students. The normal adult females were pupils of a Massage Training School, who kindly volunteered for investigation. These subjects were chosen as it had previously been found (unpublished) that hospital nurses as a class could not be regarded as strictly normal, for not only are they living under quite different conditions from all other groups studied, but on biochemical grounds also they tend to differ from the massage women investigated, who may be regarded as perfectly fit subjects. (See later.) The cases of normal pregnancy were all attending the ante-natal centre at Queen Mary's Hospital, and we are indebted to Mr. L. Carnac Rivett, F.R.C.S., for permission to investigate them. The normal children, and both the debilitated children and adults, were selected from amongst the patients attending the medical out-patient department of one of us (A. A. O.) at the above hospital. It would, of course, have been better to have selected our normal children from private preparatory schools, where conditions are most likely to approach the ideal, but as this proved impracticable we were compelled to select from amongst the fittest children attending as out-patients mostly those with such local conditions as ringworm, but who appeared to be healthy in other respects. It is important to remember that under such conditions it is not always easy to decide when a child is to be regarded as strictly normal. Owing to their great physical activity and emotional instability, it is scarcely surprising that the biochemical make-up in childhood is of a relatively unstable pattern, and that some of the blood constituents, including the bicarbonate, show considerable fluctuations over short periods. For these reasons it

is necessary to pay great attention to the conditions under which the blood sample is taken from children, i. e. the time in relation to the last meal, the composition of the latter, preceding exercise, excitement, and so forth. A certain number of 'normal' children were recruited from amongst the families of 'patients'. All the children were attending elementary day schools and were between the ages of six and twelve years inclusive. The debilitated children were of the same class and age as the controls, and attended hospital complaining of such minor symptoms as lassitude, headache, &c., a detailed list of which has been given elsewhere (4), and it is only necessary to point out that cases of 'debility' following definite organic disease, such as measles and tonsilitis, were not included. In brief, it may be said that the subnormal children under consideration were those who in appearance, colour, stance, behaviour, and with reference to their symptoms would be classed on sight by a trained observer as being a little below par.

In the group of debilitated adults, females only were investigated, as most male patients attend for frank organic disease. The blood sample was always taken in the intermenstrual interval, i. e. at any time other than a week before or a week after the menstrual period. From this group, too, cases with a history of recent definite illness, or presenting gross sepsis, dental or otherwise, were also excluded. The symptoms for which these patients attended hospital included: headache, pallor, constipation, indigestion, flatulence, lassitude, weakness, insomnia, worry, depression, 'puffiness' or swelling of the ankles, 'amenorrhoea', 'rheumatics', 'anaemia', and others. All the patients attended at regular intervals for a period of six months and were watched in order to make certain that the symptoms complained of were not the earliest manifestations of undiscovered organic disease, which might become obvious later. These cases, which constitute the bulk of those seeking advice at the medical outpatient department of any general hospital, are perhaps best defined by the term 'debility' itself. The procedure adopted in all cases was for one of us (A. A. O.) to make a careful clinical examination, which included the usual urine tests, to exclude gross organic disease. Each patient was then given a numbered card. Blood was taken by the collaborator (H. G. C.) and the sample given a corresponding number. In dealing with the children, a diagnosis of either 'normal' or 'subnormal' was made and entered on the history sheet and not on the numbered card. It is believed that in this way personal bias in correlating the biochemical and clinical findings has been reduced to a minimum.

Variations in the Plasma Bicarbonate in Health and in Debility.

The average plasma bicarbonate in each group will be seen in Table I and in the charts which follow. The bicarbonate tends to decrease in the several groups in the following order, being highest in the normal adult males, normal

adult females in the intermenstrual periods, normal children, normal adult females during menstruation, debilitated children, debilitated adult females, and lowest in normal pregnancy. Although the difference in value between some of the groups is not great, there is a definite shift to the acid side in the order mentioned. This is shown best in the accompanying charts.

TABLE I. *Plasma Bicarbonate in all Groups.*

| | | NaHCO$_3$ Molar. | | |
Group.	No. of Cases.	Highest.	Lowest.	Average.
Normal adult males	86	0·0340	0·0280	0·0320
Normal adult females (intermenstrual)	31	0·0317	0·0280	0·0300
Normal adult females (menstrual)	31	0·0321	0·0260	0·0291
Normal pregnancy	68	0·0305	0·0210	0·0247
Normal children	38	0·0320	0·0265	0·0299
Debilitated adult females	72	0·0320	0·0205	0·0271
Debilitated children	68	0·0315	0·0225	0·0275
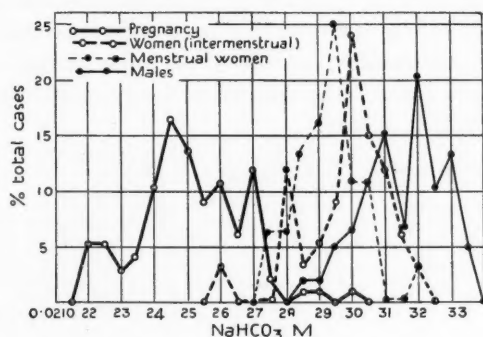
CHART I.

Chart I shows the average plasma bicarbonate in each of the 'normal' adult groups investigated. It will be seen that women in the intermenstrual period are slightly more 'acid' than men, a fact noted earlier by Cook and one of us (5), and this is even more marked during the menstrual flow. The bicarbonate of the blood is considerably reduced throughout the whole of pregnancy in at least 80 per cent. from the eighth week onwards, and, in a considerable number, even earlier than this. That the plasma bicarbonate in normal males is not subject to great variations in ordinary circumstances is shown by the fact that repeated observations (20) on one of us (A. A. O.) over a period of five years has given the following results: average = 0·0320 molar, highest = 0·0336 M., lowest = 0·0304 M., and twelve observations (on H. G. C.) over a period of three years gave values of: average = 0·0323 M., highest = 0·0331 M., lowest = 0·0299 M. The consistency of these results is remarkable when it is recalled that the concentration of the plasma bicarbonate is dependent upon such variable factors as the renal and respiratory activities, &c. In healthy women the bicarbonate appears to be subject to greater variations, even when only intermenstrual samples are considered; thus in one subject intermenstrual values of 0·0290,

0·0260, 0·031, 0·0276 molar were obtained on successive occasions, a finding which was confirmed in other cases. Further details of the values obtained in normal menstrual and intermenstrual females have already been published (6).

It has been previously stated that hospital nurses cannot be regarded as suitable subjects to use as 'controls'. In a series of nurses from two London hospitals the average plasma $NaHCO_3$ (intermenstrual) = 0·0288 M., highest = 0·0301 M., lowest = 0·0267 M. As will be seen from the charts and tables, these figures suggest some degree of subnormality, although none of the subjects complained of ill health.

A further point of interest arises from a study of the plasma bicarbonate in old age. Through the courtesy of the authorities this was investigated in eight females between the ages of 71 and 90 years of age inclusive, inmates of a London workhouse, and in whom senility was the only obvious feature. The average $NaHCO_3$ = 0·0319 M, highest = 0·0331 M., lowest = 0·0310 M. It is, of course, not possible to draw conclusions from such a small number of cases, but should these figures be confirmed in a larger series, it would suggest that in women the bicarbonate which is, on the whole, lower during the child-bearing age than in the male, becomes the same as in the male at some time after the menopause, or at least in old age.
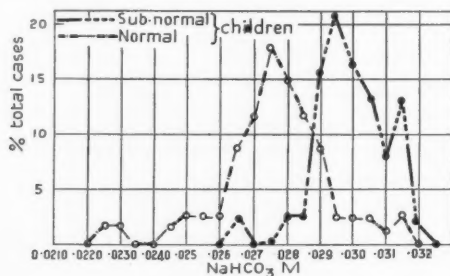

CHART II.

Chart II contrasts the plasma bicarbonate in thirty-eight normal and sixty-eight subnormal or debilitated children. It will be seen that some degree of acidosis is the rule in the debilitated. None of the normal children had acetonuria at the time the blood sample was taken. Of the subnormal children, ten, or 16 per cent., had mild acetonuria (positive Rothera but negative $FeCl_3$) at the time. In four of these an attempt was made to estimate the amount of total acetone bodies in the blood by the method of van Slyke and Fitz (7), but no excess of these substances was found.

It was concluded that the acidosis of debilitated children was not generally due to, nor associated with, ketonaemia (8). Incidentally, no difference was noted between the two sexes in these children as regards the $NaHCO_3$ content of the plasma.

In Chart III the plasma bicarbonate in seventy-two debilitated women is compared with the normal adult females. The samples in both groups were

intermenstrual. It will be seen that acidosis is again the rule in the debilitated subjects.

In Chart IV the plasma bicarbonate in all the groups studied is compared. To avoid confusion, the irregularities of the individual curves for each group have been omitted.
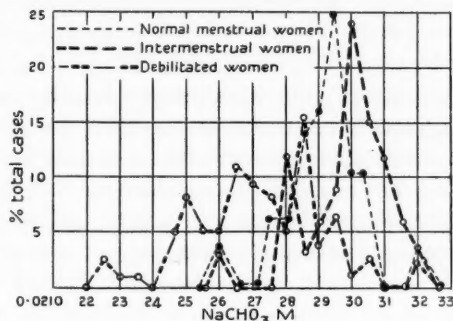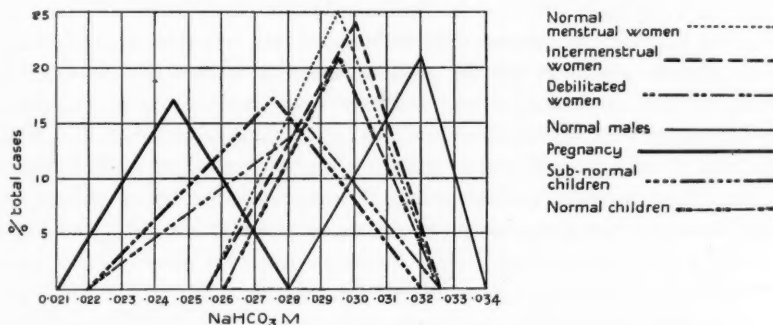

CHART III.

CHART IV.

It will readily be seen that the plasma bicarbonate is on the average highest in normal adult males, becoming less in the other groups in the following order: normal intermenstrual females, normal menstrual females, normal children, debilitated adult females, debilitated children, and lowest in normal pregnancy. The curves also show the considerable degree of 'acidosis' which occurs in both debilitated adults and children. Whatever the underlying causes of this condition of acidosis, and the chemical or physical explanation, it is clear that this type of acidosis is extremely prevalent amongst the class of patient under consideration, at least in London, for, as already mentioned, there is reason to believe that the cases selected constituted a representative sample. It may be said, therefore, without fear of contradiction, that a not inconsiderable proportion of the population is suffering from varying degrees of acidosis as defined herein. That such a condition is of more than academic interest will appear from what follows. Here it is desired to emphasize two points. First, that it is not suggested that the acidosis is the direct cause of all the varied

symptoms of debility enumerated above, though, as will be seen later, it is apparently responsible for some of them ; secondly, the demonstration of the prevalence of this condition must not be regarded as a justification for the indiscriminate use of alkalies in any form—a practice which is generally useless, often harmful, and which cannot be too strongly condemned.

The Plasma Chlorides.

As all the cases investigated were out-patients, it was not possible to obtain 24-hour specimens of urines, and also, as there was not any control over the diet, the output of chlorides and water in these cases could not be studied. In many of the cases, however, the plasma chlorides were estimated, and the figures are of some interest, though no very definite conclusions can be drawn from them. The average plasma chlorides in each group will be seen in Table II. On the whole, as will be seen from Table III, it may be said that there is a tendency for the chloride values to be lowest in those groups with the highest plasma bicarbonate, and vice versa, but the parallelism is upset by the relatively high chlorides in both normal and debilitated children. The differences between the several groups, however, are not marked, and for the reasons already given we do not wish to stress these chloride values. Incidentally, a chloride estimation was performed on a single specimen of urine in each case at the time the blood sample was taken. This, of course, is of doubtful value, but it may be said that, comparing the total of these with the corresponding blood chlorides in each group, it was found that, on the whole, with a high blood chloride, the urinary chloride value was also high, and vice versa.

TABLE II.

Group.	No. of Cases.	Plasma NaCl grm. per 100 c.c.		
		Highest.	Lowest.	Average.
Normal adult males	—	—	—	—
Normal adult females (intermenstrual)	31	0·620	0·541	0·585
Normal adult females (menstrual)	31	0·623	0·547	0·591
Normal pregnancy	30	0·623	0·572	0·596
Normal children	27	0·638	0·587	0·606
Debilitated children	33	0·638	0·576	0·608
Debilitated adult females	30	0·617	0·558	0·594

TABLE III.

Group.	Average NaHCO$_3$ (Molar).	Average NaCl (grm. %).
Normal adult males	0·0320	0·587
Normal adult females (intermenstrual)	0·0300	0·585
Normal adult females (menstrual)	0·0291	0·591
Debilitated females (intermenstrual)	0·0271	0·594
Normal pregnancy	0·0247	0·596
Normal children	0·0299	0·606
Debilitated children	0·0276	0·608

Again, no difference was noted between the sexes in the children as regards the chloride content of the plasma.

The tendency for the plasma chlorides to be lowest in those groups with the highest plasma bicarbonate, and highest in those with the lowest bicarbonate, is of interest in view of the experiments of Haldane and his co-workers (9), who showed that in the acidosis (reduced bicarbonate) following the ingestion of ammonium chloride, the bicarbonate of the plasma was replaced by chloride almost molecule for molecule. It will be noticed that the average plasma chloride of the debilitated adult females is not very much greater than in the normal intermenstrual females. Of the debilitated women, a considerable number had low values for both bicarbonate and chloride.

If the pH of the blood were lower in these cases, it appeared possible that an increase in the cell chlorides might account for the low plasma chlorides. In a few of these cases, however, estimation of the whole blood chlorides failed to support this view, but, as stated above, the pH was not estimated, and we are not prepared to dismiss this possibility until further observations have been made under better controlled conditions.

The Water Content of the Body in the Several Groups.

Our observations on this point are almost entirely clinical. In a considerable number of cases the intradermal salt test of McClure and Aldrich (10) was employed, and, although we have in the main been able to confirm their results in cases of definite disease, the end-point of the method was found to be too uncertain, at least in our hands, for the finer differences in water content which occur in debilitated persons. Attention was first drawn to the prevalence of mild degrees of oedema in hospital out-patients suffering from debility by noting the frequency with which females of this type complained of swelling of the ankles during the menstrual periods. Later, one of us (A. A. O.) was in charge of a clinic for the investigation and treatment of cases of Bright's disease, and not infrequently such cases of unexplained oedema, unaccompanied by albuminuria, were sent up as anomalous forms of nephritis. Investigation of the renal functions by the usual tests showed nothing abnormal, and it soon became apparent that these cases were, in reality, well-marked examples of waterlogging of the tissues occurring in debilitated individuals. Blood counts in these cases proved that the condition was not due to anaemia. Further experience has shown that mild degrees of non-albuminuric oedema are extremely common. The condition only occasionally occurs in males, but frequently in debilitated women, in whom it may persist, with exacerbations at the monthly periods. In milder cases, visible and palpable oedema is present at or about the menstrual epoch only (11). In this connexion it is interesting to recall the observation of Widal that, until oedema is present to the extent of 6 kg. of excess water in the adult, it does not become clinically apparent, at least by palpation. The type of oedema referred to above is most often seen in the feet, ankles, and legs, and is most marked towards evening, probably owing to the effect of gravity. Some degree of waterlogging of the tissues is almost

a constant feature of all cases of pregnancy, normal and abnormal, especially in the later months. Many observers (12) have demonstrated an increased water content of the serum in normal pregnancy, and our own observations with the intradermal salt test support the view that throughout pregnancy there is a higher water content of the tissues—at least, in a large percentage of cases. Clinical experience, too, shows the frequency with which gross, i. e. palpable, oedema occurs in the later months of pregnancy, which often precedes the appearance of albumen in the urine by some weeks. An increased water content of the tissues therefore occurs most often in pregnancy, very frequently in debilitated females, occasionally in normal females at the menstrual times, and practically never in normal males. Or, in other words, most frequently in those groups with the lowest plasma bicarbonate and, conversely, least often in the groups with the highest bicarbonate.

In children the position with regard to the water content of the body is rather different (cf. the relatively high plasma chlorides in childhood).

Clinically, oedema of the type which pits on pressure is rare in childhood, except in cases of nephritis. Normally, children show a higher tissue water content than adults, as measured by the intradermal salt test; and it has been shown by Baker (13) and Harrison (14), using this test, that in children suffering from acute infections such as scarlet fever, diphtheria, and pneumonia, the water content of the body is still further increased. Again, it has long been known that many of the tissues and organs of the body contain a higher percentage of water in childhood than in adult life, as shown by ash analyses (15).

Speaking generally, therefore, it is true to say that, in the groups of normals and subnormals under discussion, the lower the bicarbonate the higher the water content of the body, and, with the exceptions noted previously, the higher the plasma chlorides. These relationships are shown in Table IV.

TABLE IV.

Group.	Average NaHCO$_3$ (Molar).	Average NaCl (grm. %).	Water Content.
Normal adult males	0·0320	0·587	least
Normal adult females (intermenstrual)	0·0301	0·585	+
Normal adult females (menstrual)	0·0291	0·591	+ +
Normal children	0·0299	0·606	+ + +
Subnormal children	0·0276	0·608	+ + +
Subnormal adult females	0·0271	0·594	+ + + +
Normal pregnancy	0·0247	0·596	+ + + +

As already mentioned, in the absence of any records of the total intake and output of either water or salts, there is not any evidence of either water or chloride retention in the true sense of the term in any of these groups, and certainly no evidence of any associated renal defect in this respect.

It is therefore submitted that in the normal groups the evidence shows that there is a tendency for those with the highest plasma NaHCO$_3$ content to have the lowest plasma chlorides, and the least body water content, and vice versa, whilst in debility, both in adults and in children, there is a tendency

towards a lowered plasma $NaHCO_3$, increased plasma chloride, and water content. In childhood the latter is more evenly distributed throughout the organs and tissues, and is not generally present as 'oedema', especially of the subcutaneous tissues, the form in which it commonly occurs in adults.

To summarize, it may be said that, in general, the lower the plasma bicarbonate the higher the water content of the body. It is clear then that the type of acidosis described is very frequent, and it remains to discuss in what manner, if at all, it is either directly or indirectly responsible for any of the varied symptoms of 'debility'.

Variations in the Plasma Bicarbonate in Disease.

During the past few years, for reasons unconnected with the subject of this paper, we have estimated the plasma bicarbonate in a considerable number of different diseases. The average values obtained in some of them are given in the following table.

TABLE V.

Disease.	No. of Cases.	Plasma $NaHCO_3$M.		
		Mean.	Highest.	Lowest.
Addison's anaemia	8	0·0278	0·0302	0·0232
Cirrhosis of liver	9	0·0283	0·0365	0·0223
Active rickets	7	0·0219	0·0284	0·0174
Acute rheumatic fever	17	0·0290	0·0333	0·0261
Active chorea	19	0·0297	0·0365	0·0258
Gout, active chronic	13	0·0276	0·0325	0·0226
Gastro-duodenal ulceration	15	0·0307	0·0338	0·0272
Active pulmonary tuberculosis (no dyspnoea)	6	0·0312	0·0332	0·0295
Bronchial asthma (between attacks)	11	0·0279	0·0308	0·0245
„ „ (during attacks)	10	0·0338	0·0380	0·0275

Although it would be unwise to dogmatize from the figures obtained from such comparatively small numbers of cases as those cited above, there would seem to be evidence that some degree of 'acidosis' is the rule in Addison's anaemia, cirrhosis of the liver, chronic active gout, and active rickets, whereas it appears to be exceptional in acute rheumatic fever, active chorea, gastric and duodenal ulceration (active), and early active pulmonary tuberculosis. The above figures on the whole agree with those of other workers in the several diseases mentioned. The figures for bronchial asthma would suggest that a decreased plasma bicarbonate is more commonly found between attacks than in normal persons, but the cases investigated were nearly all of the 'hospital class', and it is therefore not justifiable to conclude on this evidence alone that 'acidosis' is the rule, and provides the 'soil' upon which this condition flourishes. Such a possibility requires further investigation. The high values given during the attacks undoubtedly represent a relative alkalosis due to the dyspnoea.

The type of acidosis under discussion is, therefore, not only extremely prevalent amongst cases of debility, but is also found in quite a number of well-recognized and common diseases of entirely different origin, and characterized by widely different symptoms. It should be noted, too, that in practically no

disease or condition in which this type of acidosis has been found has a really satisfactory explanation of its nature been offered, with the possible exception of diabetes mellitus, in which it is sometimes fully, or almost fully, accounted for by the amount of acetone bodies found in the blood. The acidosis of nephritis, for example, is often attributed to retention of phosphates and sulphates in the blood, but recent (unpublished) observations show that, except as a terminal event in some cases, this is not generally so. Estimations of the blood uric acid by the method of Folin (16), in the cases of gout quoted above, proved that here too the acidosis present was not due entirely to excess of this substance in the blood. The most plausible explanation yet offered for this condition is that of Y. Henderson (17), who describes it as a 'driving out of alkali from the blood into the tissues, or the reverse process of calling it back into the blood, by alterations in the respiratory exchanges'—an explanation which receives considerable support from the observations of Mann and Scott (18), who have shown that a decrease in the plasma bicarbonate is common in certain types of mental disease, and is due to, but is not the cause of, alterations in the sensitivity of the respiratory centre. It is also important to remember that the term acidosis as used herein does not mean acid poisoning in any sense; and as Henderson says, 'a decrease of blood alkali is probably in most cases merely incidental to something more fundamental. An excess of acid is probably not even an essential, or much less a fundamental, feature of it, but merely a secondary and not invariable result'. Here, then, is a pathological state, the exact cause of which is not known for certain, and which occurs with great frequency in a large number of quite different diseases. In view of the evidence already submitted concerning the relationship between the plasma bicarbonate and the water content of the body, it may be of interest to consider to what extent, if any, an acidosis and the associated waterlogging may modify the functions of the body as a whole, or of any of the organs, in debility and in frank disease; also, whether such a state may not be an important factor in lowering resistance to infection, and play some part in increasing the severity and delaying recovery in a large number of diseases. An attempt has been made to investigate some of these problems, and it is hoped to publish the results obtained in due course.

Conclusions.

1. That there are significant biochemical differences, especially in respect of the bicarbonate content of the plasma, and of the water content of the body, between normal men, women, and children.

2. That in debilitated persons, both adults and children, some degree of acidosis is the rule, and this is often accompanied by an increased water content of the body.

3. That this condition of 'acidosis' is widely present amongst persons of all ages of the so-called 'hospital classes' of this country.

4. That the type of acidosis described is not due to, nor associated with, excess of ketone bodies in the blood.

5. That, speaking generally, the water content of the body tends to vary inversely with the plasma bicarbonate.

6. That persons of the 'hospital class', even when not suffering from recognizable disease, do not constitute suitable material from which to select controls for biochemical standards of normality.

7. That many published figures relating to the acid-base balance of the blood, suggesting evidence of an 'acidosis' in numerous diseases, are of doubtful value when the estimations have been carried out upon 'hospital class' patients, as hitherto, so far as we are aware, the normal for this group has not been established.

We should like to take this opportunity of thanking Prof. R. Donaldson and Dr. Arthur Davies, Directors of the Pathological Laboratories at Guy's Hospital and Queen Mary's Hospital, respectively, for laboratory facilities, and those students at Guy's who volunteered for investigation. Also Dr. A. C. Hampson for much helpful criticism.

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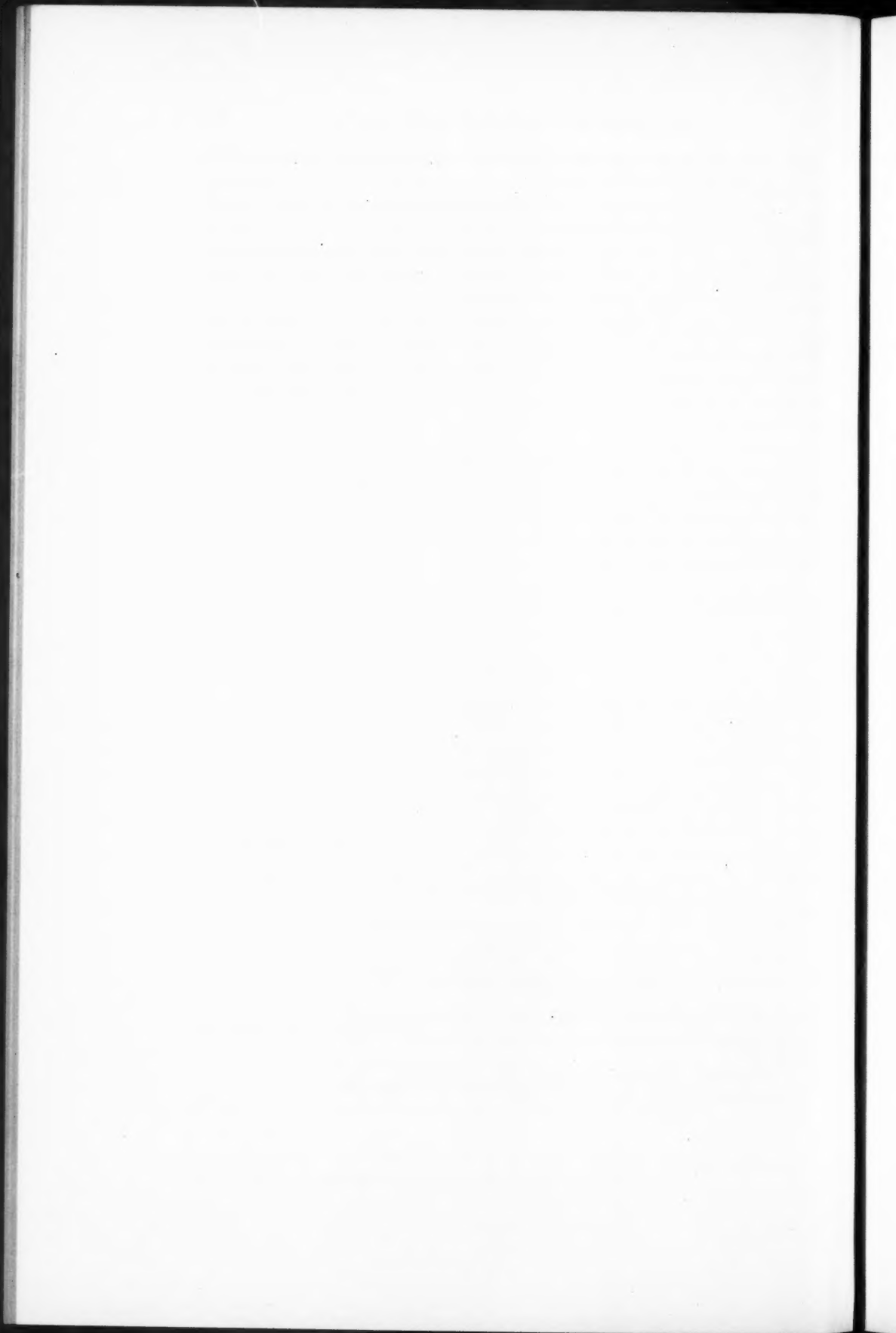
CARCINOMA OF THE LUNG CAUSING INTESTINAL OBSTRUCTION BY SECONDARY DEPOSITS [1]

By W. G. BARNARD and T. R. ELLIOTT
(From University College Hospital)

With Plates 17–20.

CANCER of the lung is generally admitted by pathologists to have become more common in recent years. This increased incidence has naturally brought the disease into the foreground as a possibility that must always be considered in the differential diagnosis of many forms of intrathoracic malady. But its clinical diagnosis is usually centred on obvious lesions in the chest and, in spite of the fairly wide dissemination which may be found at necropsy, is seldom deviated to some secondary extrathoracic deposit which is the immediate cause of the patient's symptoms.

It has, however, been recognized for some time that all cases of tumour in the brain or of progressive destruction of the vertebral column with symptoms of spinal cord lesions must be closely examined for the chance that these patients may actually be suffering from a primary lung growth. So, too, it is recognized that malignant disease of the liver may occasionally be secondary to lung cancer, though in this instance the diagnosis has not the same importance in respect of proposed operative treatment as it has for secondary deposits in the brain or vertebral column.

The incidence of secondary metastases as proved at necropsy is well displayed in the analysis by S. L. Simpson (1) of 139 cases of primary carcinoma of the lung which had been examined at the Pathological Institute of the London Hospital. To select some of his figures, such metastases were found in:

Extrathoracic lymphatic glands, 70 cases out of 139.

Liver, 45 cases out of 139.

Vertebrae, 29 cases, of which 7 had paraplegia or cord features, while the primary lung focus was not diagnosed in 5 of these.

Brain, 19 cases, and the primary lung focus was not diagnosed in 11 of these which showed the features of cerebral tumour.

Intestines, 8 cases, but none of these showed any related intestinal symptoms, and the secondary deposit was only recognized at necropsy.

The two cases described in the present paper did come forward clinically as examples of intestinal tumour, one being operated on for obstruction at a time

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[1] Received March 6, 1930.

when there was no suspicion of lung cancer as the primary source.   It is obvious that the decision as to surgical treatment of an intestinal neoplasm might be seriously influenced by knowledge that the growth was secondary to a primary in the lungs; and these cases do show that this problem may arise in clinical experience.   We have not found any similar cases described in published papers on cancer of the lung; but if the main disease becomes still more prevalent, it is likely that examples of intestinal secondaries may be found to be less rare than they at present appear to be.

Case 1.   A man, aged 48, was admitted to hospital in July 1929 with a history of three attacks of abdominal pain, and vomiting having occurred in the last five weeks.   He had also lost weight and was thin (8 st. 11 lb.: height 6 ft.). No signs of disease were found in the chest, and there was no sputum and no history of lung trouble.   The symptoms pointed to progressive obstruction of the small intestine, and laparotomy found a growth obstructing the ileum seven inches above the caecum.   The loop of bowel was excised in two stages, but the patient died of early local peritonitis and acute broncho-pneumonia the day after the excision was completed.

In the loop of bowel (Fig. 1) removed at operation there was a growth almost completely encircling and greatly diminishing its lumen.   The bulk of the growth was in the wall of the gut, and the mucosa, while slightly ulcerated over the most prominent part, had almost entirely escaped infiltration.   On microscopic examination the growth (Fig. 2) proved to be a squamous and prickle-celled carcinoma, and chiefly on the grounds that the mucosa was so little affected and that no part of it showed evidence of squamous-celled metaplasia it was reported as a secondary growth.

Necropsy revealed a mass of firm granular milky-white carcinoma arising in the origin of the main bronchus to the lower lobe of the right lung and spreading along the walls of its branches for about 2 cm.   There was direct spread to the adjacent pericardium and pulmonary vein, with a pinhead mass protruding through the intima of the vein.   Distal to the growth, the right lung showed purulent bronchitis, slight bronchiectasis, and patches of bronchopneumonia.

The left lung showed only mucopurulent bronchitis, with congestion and oedema.   The other organs of the body, including the prostate, showed nothing of importance to the diagnosis.   Microscopic examination failed to find any secondary carcinoma in the bronchial and coeliac lymphatic glands.

The main growth in the lungs was a squamous prickle-celled carcinoma (Fig. 3) similar in all respects to the microscopic appearance of the mass in the bowel.   It had the general characteristics of a primary bronchial carcinoma, for it infiltrated all the walls of the bronchus and spread along these walls, while it also infiltrated the pericardium and pulmonary vein.

Although squamous-celled carcinomata may arise in the small intestine they do so far less frequently than in the bronchi.   The distribution of the growth in the two situations in this instance provides strong evidence for the view that it was primary in the bronchus and that the symptoms were due to a secondary metastasis in the ileum.

Case 2.   The evidence in this case, that a primary tumour of the lung produced a metastasis in the intestine, was not quite so clear as in the first patient.

A man, 67 years old, also admitted to hospital in July 1929, gave a long history of indigestion with abdominal pain and with recent loss of weight. Eighteen months earlier he had been examined by X-rays at another hospital and a duodenal ulcer diagnosed.   In February 1929 an attack of 'influenza'

was followed by cough and some signs persisting in the upper right lung. Abdominal pain then became more frequent, but there was no vomiting.

A tender, immobile, hard mass was readily palpable in the region of the caecum. No enlarged glands were felt, but a small tender nodule was found just under the skin over the first lumbar vertebra, and there was another close to the spine of the scapula. Occult blood was present in the stools. There were physical signs pointing to fibrosis of the right lung, and the sputum contained tubercle bacilli.

The subcutaneous nodules suggested the diagnosis of cancer of the colon rather than tuberculous ulceration and induration in the bowel; but histological examination of one of the nodules that was excised for this purpose led to a different opinion. The section showed (Fig. 4) solid trabeculae and irregular masses of oval and short spindle cells having the appearance and arrangement of an ' oat-celled ' carcinoma of bronchus (2). A tumour of this kind arising in the colon had not been encountered by us before, so it was thought that the primary was probably in the lung.

The patient steadily lost strength, but the signs in the chest were never definitely conclusive of the presence there of primary new growth. The radiogram showed deviation of the trachea to the right and an irregular cavity in the upper lobe with dense infiltration near it. The right lower lobe was irregularly opaque and there was an enlarged mass at the hilum. The general appearance was compatible with that of tuberculous infection. Scattered throughout the lung fields on both sides were some small, round shadows, which were almost certainly secondary nodules of growth. These would have been regarded as secondary to a cancer of the colon if it had not been for the contrary evidence obtained by microscopic study of the subcutaneous nodule.

Constipation and abdominal distension became more troublesome, but the intestinal obstruction was never so intense as to compel operation. The patient died at the end of September.

At post mortem a small ulcerated carcinoma in the second part of the duodenum, a larger one in the upper part of the jejunum (Fig. 5), and a large ulcerated growth completely encircling the lumen of the ascending colon (Fig. 6) were found.

In the right lung the origin of the main bronchus to the posterior part of the *lower* lobe was surrounded by a mass of firm, yellowish-white growth about 2 cm. in cross section. Immediately below and behind the apex of the right upper lobe was a plaque (4 × 3 × 2·5 cm.) of granular milky-white growth marbled with soot, and this lay in the lower and anterior part of a ragged walled tuberculous cavity (5 × 4 × 4 cm.). Small patches, about 1 cm. diameter, of caseous tuberculosis, and others of grey gelatinous mucous carcinoma, were scattered throughout the lower and middle lobes, and there were larger similar patches in the neighbourhood of the big cavity with its plaque of growth.

The left lung showed only a few small nodules of growth scattered in the upper lobe. The bronchial and lumbar lymphatic glands were infiltrated with growth, and there were secondary deposits also in the pancreas and kidneys, while there was a large mass, 2 cm. in diameter, adherent to the diaphragm above and deforming the surface of the spleen. The liver was free from growth. On histological examination the growths in the small and large intestine (Fig. 7) and in the bronchus (Figs. 8 and 9) were all composed of irregular groups of oval and spindle-shaped cells similar to those found in the subcutaneous nodule. The small growth in the duodenum appeared to be a recent deposit, and there was no evidence of its being related to the duodenal ulcer that had been supposed to exist eighteen months earlier and of which no evidence was found at necropsy.

If that completed the story it would afford another fairly straightforward example of secondary carcinoma in the intestine from a primary bronchial growth; but unfortunately the picture was complicated by the discovery of

many patches of mucus secreting columnar-celled carcinoma (Fig. 10) near the tuberculous foci in the right lung.

Sections from different parts of the growths in the bowels were examined, but in none of them nor in any other of the growths outside the lung could columnar-celled carcinoma be found. This is not conclusive evidence against the origin of the tumour from the colon, but it must be rare for a carcinoma of the colon to behave in this way. On the other hand, primary tumours of bronchi do commonly show great variety in cellular structure. The distribution of the secondaries apart from the intestinal growths, that is in the other lung, lymphatic glands, diaphragm, pancreas, and kidney, was such as is commonly associated with carcinoma of bronchus and not with carcinoma of colon.

Despite the two types of growth in the lung, we are therefore of the opinion that this was also a case of primary carcinoma of the lung with multiple secondaries in the intestine and a complicating pulmonary tuberculosis.

Summary.

Two cases are described in which the obvious clinical picture was that of intestinal tumour causing obstruction. These tumours were, definitely in one case and probably in the other, secondary deposits from primary carcinoma of the bronchus.

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DESCRIPTION OF PLATES 17–20.

FIG. 1. The loop of ileum removed at operation in Case I. The intact mucosa can be traced over the greater part of the growth.

FIG. 2. Section of the growth of Fig. 1, showing the intact mucosa and infiltration of the submucosa by squamous-celled carcinoma.

FIG. 3. Squamous prickle-celled carcinoma in the lumen and wall of the bronchus in the right lung of Case I.

FIG. 4. A section of the subcutaneous nodule in Case II, showing the solid trabeculae of oval and spindle-shaped cells with deeply stained oval nuclei.

FIG. 5. The nodule of secondary carcinoma in the submucosa of the upper part of the jejunum in Case II.

FIG. 6. The large ulcerated growth in the first part of the ascending colon, Case II. A white rod marks the ileo-caecal opening.

FIG. 7. The spindle and oval-celled growth in the submucosa of the colon, Case II.

FIG. 8. 'Oat' celled growth in the wall of the bronchus, Case II.

FIG. 9. A high power view of the same section as Fig. 8. The 'oat' cells with their oval nuclei are shown.

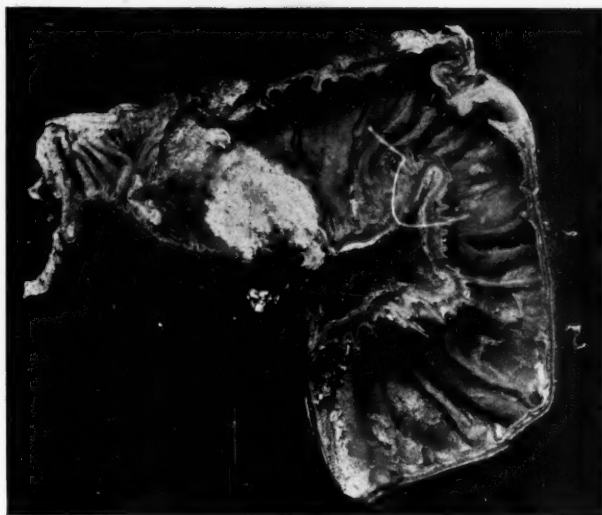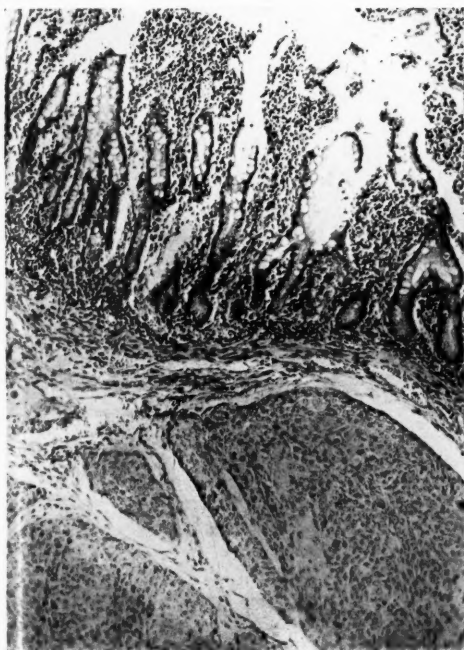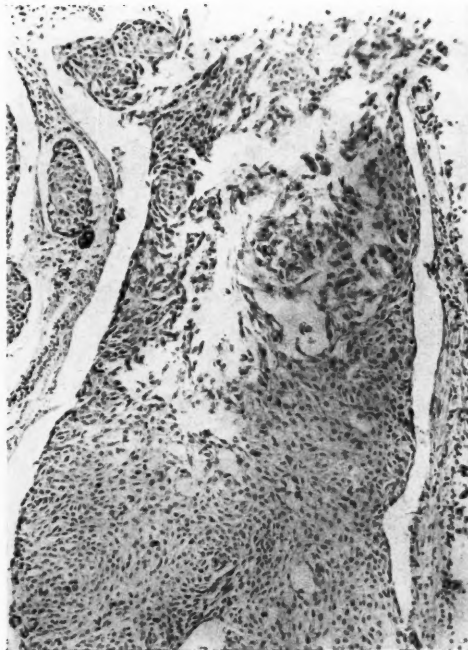FIG. 10. Alveoli of columnar mucus secreting carcinoma in the periphery of a tuberculous focus with giant cell system, Case II.
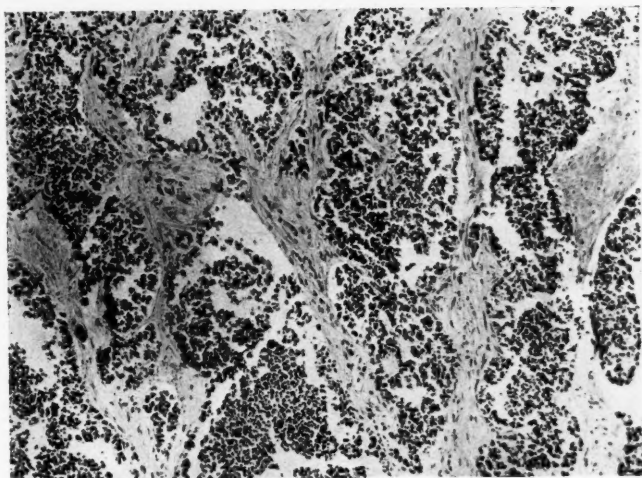
FIG. 1

FIG. 2

FIG. 3

Fig. 5

Fig. 6

Fig. 8
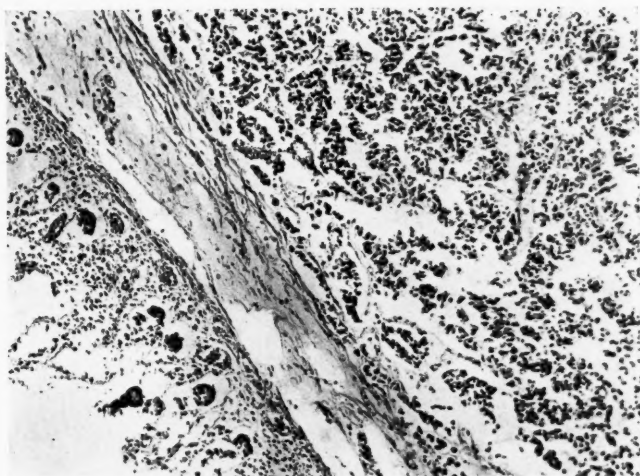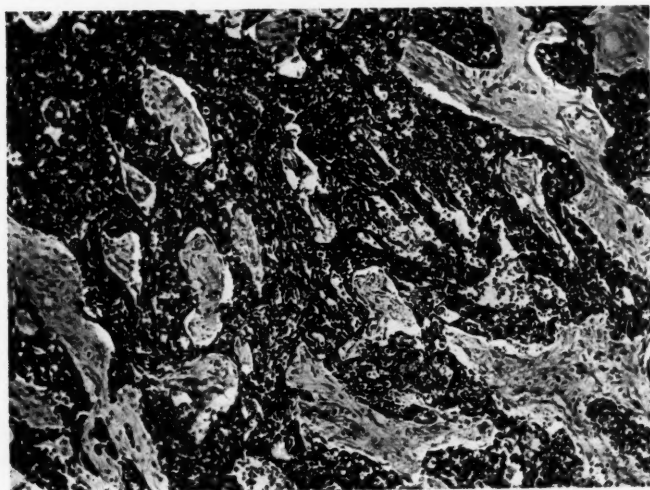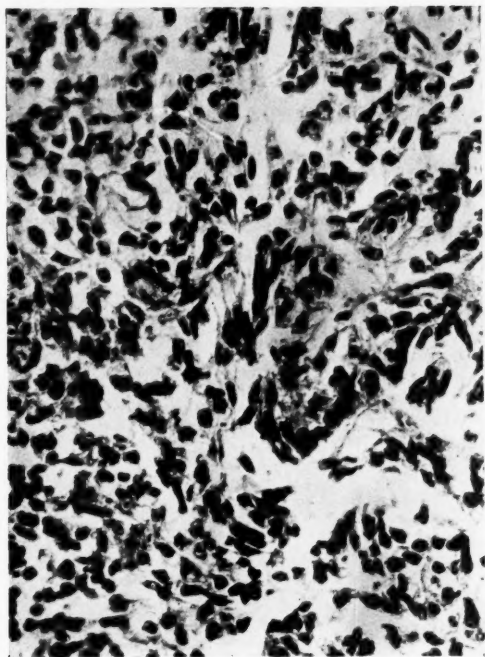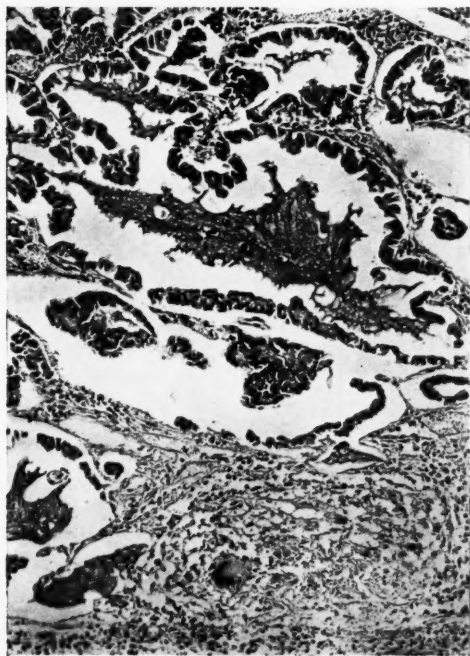
Fig. 7

Fig. 4

Fig. 9

Fig. 10

STUDIES ON SPRUE WITH SPECIAL REFERENCE TO TREATMENT [1]

BASED UPON AN ANALYSIS OF 200 CASES

By PHILIP MANSON-BAHR and HUGH WILLOUGHBY
(From the Hospital for Tropical Diseases, London)

With Plates 21–23

FROM a survey of the literature on sprue during the last ten years, we have been impressed by the large amount of work which has been expended upon the etiology of this disease from the bacteriological standpoint and the negative value of much of this evidence. There has been an absence of any systematic or minute observations on the symptomatology conducted over a long period of time. In order to fill up this gap we have endeavoured in these studies to correlate the various symptoms with the idea of clarifying the mind regarding the underlying pathological processes which may in some manner point to the basal etiological factor of this mysterious disease. At the same time we have endeavoured to compare various methods of treatment, and by these means to attempt to explain the value of different drugs and diets in overcoming the symptoms of sprue.

While freely acknowledging the gaps in our investigations, we consider that our work may be of some value, as it consists of a systematic and comparative study of a large number of cases.

It has fallen to few to be able to avail themselves of so much clinical material spread over a period of ten years, and our object has been to obtain bed-rock facts which may in the future lead to more elaborate biochemical investigation on disputed points. Again, there is no agreement as yet regarding the basal pathological processes that would satisfactorily account for the well-known cardinal signs and symptoms of sprue. In this paper it has been our endeavour to elucidate some of them.

Source of Clinical Material.

Our series of 200 cases have been admitted to the Hospital for Tropical Diseases in all stages of the disease; a certain proportion have applied directly to the hospital for admission, while others have been recommended by practitioners from abroad, while quite a large proportion have been treated as private patients.

[1] Received February 21, 1930.

E e 2

The cases have come from all classes of the community who, having acquired the disease in the tropics, have returned to England for treatment. It comprises the educated classes, such as Government officials, travellers, missionaries, seafaring people, and also the native Indians.

From a study of the subjoined table it appears, as has been well understood in the past, that sprue is pre-eminently an Asiatic disease, though it has a wide tropical, and to a lesser extent a subtropical, distribution. Considering the number of Europeans now resident in Central Africa, its rarity in that continent is a matter for comment. Sprue is therefore pre-eminently a disease of the European resident in tropical countries.

The greatest number came from India, China, and Ceylon. The record of one undoubted case from Nyasaland (1) is a feature of interest, and one from Mauritius, where the disease appears not to have been recognized heretofore. The frequency of sprue in Porto Rico, as reported by Ashford (2), its comparative rarity in Europeans from the British West Indies and from South America in our series, is to be noted.

TABLE I.

Total cases 200.   Male 135 = 67·5 %.   Female 65 = 32·5 %.
Average age 45 years.   Maximum 72 years.   Minimum 18 years.
All ages taken at time of appearance of the first symptoms of the disease.

Countries where disease was acquired —

India	.	.	.	.	.	.	97 cases
China	.	.	.	.	.	.	37 ,,
Ceylon	.	.	.	.	.	.	23 ,,
Shipping	.	.	.	.	.	17 ,, (trading in Far East)
Federated Malay States	.	.	7 ,,
Burma	.	.	.	.	.	3 ,,
British West Indies	.	.	.	3 ,,
Palestine	.	.	.	.	.	2 ,,
Philippines	.	.	.	.	.	3 ,,

1 case from each of the following :—Nyasaland, Mauritius, Venezuela, Costa Rica, Brazil, Cuba, Honduras, and Java.

This may be compared with another series of cases by G. Carmichael Low (3).

Sex and Age Incidence.

More males than females (135 to 65) were victims of the disease, but this statement requires qualification, when the relative proportion of European males to females in the tropics is considered. It (4) lends some colour, therefore, to the statement that, in reality, of the two the female is more susceptible to contract the disease than the male.

Sprue is pre-eminently a disease of adult life. This has been pointed out before (loc. cit.) by one of us, and other writers have drawn attention to the same point. The youngest patient in our series was 18 years of age, and the oldest was 72 at the time of contracting the disease. The average age of onset of symptoms of sprue in this series works out at 45·3 years.

Duration.

Sprue is, as a rule, an extremely chronic disease. The duration of sprue symptoms before the patient applies for treatment is usually long; the average time in this series was 2 years and 4 months. In England, in contradistinction to what obtains in tropical practice, cases are not seen until symptoms have been manifest for some considerable time, in our series ranging from a period of six months minimum to that of eighteen years in one extreme instance. This means that a patient can suffer from the manifestations of sprue for many years without their true import ever having been recognized.

Incubation Period.

That sprue has a definite incubation period is a fact that has hitherto not been definitely recognized. This may be as brief as three months. The proof is that visitors to Ceylon and India for a few months during the winter season who have never previously resided in the tropics have returned to England with the most definite symptoms of sprue.

Case 99. Male, aged 18. Symptoms of sprue commenced five months after arrival in Java. Gradual onset with diarrhoea and typical stools. Vomiting an early feature. Sore tongue and mouth two months after onset. Total loss of weight 35 lb. ; considerable shrinkage of liver dullness.

Case L. C. M. G. Female, aged 57. Symptoms of sprue—aphthae and stomatitis with dysphagia—commenced in March 1927 after three months residence in Ceylon on her first visit to the tropics. Diarrhoea with typical stools and loss of weight followed later. Symptoms persisted for six months after her return to England in May 1927.

On the other hand—and this is significant—the disease process may lie latent in the body without provoking any symptoms for a period of as long as twenty years. This is a phenomenon which is well brought out from a study of our cases and which manifestly demands some explanation. A latent period of six to eight years' residence in Europe before the commencement of recognizable symptoms is comparatively common, but longer intervals than this are of great rarity.

Case 60. Female, aged 57 at time of onset. Lived all her life in India up to age of 37 ; never out of England for twenty years preceding onset of sprue. Disease manifested itself by typical bowel symptoms—severe diarrhoea in early morning, copious frothy offensive putty-coloured stools, with tongue symptoms following later. Tongue glazed, aphthae present, soreness marked, oesophageal discomfort. Nausea and vomiting frequent in early stages ; marked loss of weight; anaemia slight but increasing considerably later in the disease. Skin dry and inelastic. Died during relapse eight years after onset of first symptoms.

Case 4. Male, aged 52 at time of onset. Missionary in Palestine. Not out of England for eight years preceding onset of symptoms. Onset typical, large frothy pale foetid stools 3–4 daily. Complete absence of tongue symptoms, no anaemia. Loss of weight slight. Recovered.

Case 199. Male. Medical practitioner, aged 72; in China up to fourteen years before onset of symptoms. Not abroad since return from China. Typical diarrhoea of persistent type. Anaemia very marked, loss of weight excessive, marked loss of subcutaneous fat, skin dry and translucent. Recovered and did well after blood transfusion and dietetic treatment.

This latency is to our minds one of basic importance and one to which hitherto little or no attention has been paid. There can be no question that these patients have acquired sprue infection in England (where the disease is unknown) after their return from the tropics, but rather that the specific virus of sprue lay dormant in the human body, and has been roused into activity by some as yet unascertained factor. It is only explicable on the basis of some *infective* agent which is prone to periods of activity and quiescence. On the basis of analogy we may quote the example of another well-known tropical disease—intestinal amoebiasis—in which latent periods of five to six years without evoking any subjective symptoms are comparatively common (5). But in this latter instance we are dealing with a germ of comparatively large and easily recognizable proportions, which can be demonstrated in the body even during the quiescent periods.

Predisposing Causes.

Although there are strong reasons for regarding sprue as a disease *sui generis*, yet there is incontestable evidence that other specific infections of the alimentary tract may predispose to the development of the disease. Of these, amoebic dysentery undoubtedly takes the first place. Two instances are recorded of the concurrence of these two diseases where it appeared that amoebic dysentery had merged imperceptibly into sprue. Typhoid fever takes the second place; hill diarrhoea the third; and bacillary dysentery the fourth place, and so on.

(1) *Case 120.* C. M. P. Served in Mesopotamia during the war; returned to England in 1920; on March 29, 1920, was found to be suffering from amoebic dysentery—diarrhoea, stools containing active *Entamoeba histolytica*, and cysts. Pyrexia with a temperature of 103° F. with hepatitis was present which resolved after ten injections of emetine (gr. i). After ten days' treatment the stools assumed a sprue-like character, being light in colour and copious. Hepatitis persisting, the liver was explored with a needle on April 13, but no pus was obtained. Sprue-like symptoms persisted and culminated in aphthous stomatitis six weeks after their commencement. On dietetic treatment he made a lasting recovery, and has had no sprue symptoms since.

(2) *Case 140.* R. B. Sprue symptoms commenced in India in October 1926. The patient came under treatment first on August 6, 1927. Great wasting; weight 8 st. 8 lb.; total loss 76 lb. Nausea, diarrhoea, anorexia. Stools pale and frothy, averaged seven per diem. Tongue raw, red, glazed, and sensitive. Liver dullness much diminished. Skin dry and inelastic. Considerable anaemia. In the sprue-like stools *Entamoeba histolytica* in free forms were found. Was treated for sprue by dieting and for amoebic dysentery by Emetine bismuth iodide and Yatren. Made a very good recovery after seven weeks in hospital. Regained 44 lb. in weight in seven weeks. When last seen in April 1928 was in good condition. Weight 13 st. 4 lb.

Of non-alimentary diseases a history of malaria was obtained in 36 per cent. of the series under review. Malarial infection must be reckoned as a predisposing factor, and this we believe is well recognized in Bombay. Whether this is of real etiological importance is another matter, as it is comparatively easy to obtain a previous history of malaria in any case emanating from those countries in which sprue is common ; but it is undoubtedly a factor influencing treatment.

TABLE II.

Previous illness in cases recorded.

(a)	Malaria				72 cases = 36 %		
(b)	Diseases affecting alimentary tract	.	.		81 cases = 40·5 %		
	Proved amoebic dysentery	.	.	.	54	,, }	32 %
	Suspected amoebic dysentery	.	.	.	10	,, }	
	Typhoid and paratyphoid	.	.	.	9	,,	4·5 %
	Hill diarrhoea . .	.	.	.	4	,,	2·0 %
	'Diarrhoea' unclassified	.	.	.	2	,,	1·0 %
	Bacillary dysentery .	.	.	.	2	,,	1·0 %

The question naturally arises whether hill diarrhoea and sprue are not synonymous terms and that the one is not a major development of the other. The character of the onset and the distinctiveness of the stools are common to both, and, moreover, we have been able to trace the history in five cases in whom the rather dramatic onset of hill diarrhoea merged gradually into that of sprue.

Case 41. Male, aged 56. Had spent almost thirty-six years in India. In 1917, while serving on NW. frontier, had attacks of hill diarrhoea which lasted on and off for four months. Three years later, in 1920, true sprue symptoms with aphthous stomatitis and typical frothy, bulky stools and meteorism commenced. When seen in 1924 was a typical case of sprue.

Case 61. Male, aged 50. Had spent twenty-one years on the railways in Burmah. While in Hill station in 1923 suffered from 'hill diarrhoea'. In 1924, after a period of leave in England, returned to Burmah, and within three weeks acute sprue symptoms, with aphthous stomatitis and great wasting, became evident. Was admitted to hospital in a moribund condition on April 15, 1925. The patient died 3½ days later of typical sprue anaemia.

Mortality.

In contrast to what is usually stated in textbooks, sprue is by no means a fatal disease. In our series of 200 cases we have records of only seven deaths, and even this statement requires qualification. Three cases were admitted in a moribund condition and died within two to five days of admission, while one other case died of intercurrent diabetes. This leaves us with three fatal cases out of our series—a mortality rate of 1·5 per cent.

Intercurrent Diseases.

Tertiary syphilis is frequently combined with sprue and exerts a very distinct influence on the course of the disease and is a primary factor in determining treatment. Syphilis may not be suspected by manifestation of physical

signs, but is detected by the routine performance of Wassermann reactions. In nine cases a positive Wassermann was obtained, in all of whom no improvement in the clinical condition was registrable until vigorous antisyphilitic measures had been instituted. In one a combination of a tertiary syphilitic process with a sprue tongue was observed and recognized by the characteristic appearance of both processes. As with syphilis, so with alcoholism, it is a matter of common experience that the chronic alcoholic frequently contracts sprue in an acute or peculiarly intractable form.

TABLE III. *Intercurrent illness affecting Sprue patients while in Hospital in this series.*

Amoebic dysentery	.	.	.	.	2	Neurasthenia	.	.	.	2
Syphilis .	.	.	.	.	9	Diabetes Mellitus .	.	.	.	1
Eczema .	.	.	.	.	3	Pyorrhoea	.	.	.	3
Psoriasis	.	.	.	.	1	Appendicitis (acute)	.	.	.	1
Pneumonia	.	.	.	.	1	Malaria .	.	.	.	4
Alcoholism (acute)	.	.	.	1	Duodenal ulcer	.	.	.	1
B. coli infection of the urinary tract	.	1	Septicaemia .	.	.	.	1
Peripheral neuritis	.	.	.	1	Giardiasis	.	.	.	1
Ankylostomiasis	.	.	.	.	1	Haemorrhoids	.	.	.	2
Rectal polypus	.	.	.	.	1	Scurvy .	.	.	.	1

In addition, many cases took large quantities of alcohol daily.

The supervention of some acute extraneous infection, especially when accompanied by febrile disturbance and a definite leucocytosis, sometimes exerts a remarkable influence on the course of sprue and its favourable termination.

The liability of sprue patients to develop appendicitis has already been remarked upon by several writers on this subject; but the most remarkable case we have experienced was the one of which a short résumé is given below. It seemed as if the 'flare up' of a chronic appendicitis and the subsequent surgical operation had cleared up what was already a particularly intractable case of sprue.

Case 92. A lady, aged 36, infected in India; began in 1921 with typical symptoms—sore tongue and anaemia. Seen after the symptoms had lasted for four years, she was in an advanced state of the disease, with profound blood changes and oedema of the ankles. Amenorrhoea had been present for two years. She was treated in the usual manner with diet and liver soup and began to improve, but in May 1925 developed signs of acute inflammation of the appendix, which was removed, and was found to be just about to perforate. The ballooning of the caecum was such that the contained gases had to be aspirated by means of a trochar and canula. From this time forward, and she has been seen frequently since, no signs or symptoms whatever of sprue have been noted.

We have observed two cases of sprue who were attacked by pneumonia whilst undergoing dietetic treatment for sprue. In both, the attack was acute and critical, and the remarkably rapid clinical improvement which took place immediately after subsidence of the pulmonary condition certainly left the impression that the happy termination of this intercurrent illness was in some way connected with their recovery from sprue.

Case 117. A planter from India, aged 61, had been diagnosed as sprue in 1913, but it was not till February 1926 that he applied for serious treatment.

There was marked anaemia of the pernicious type, with typical blood changes and normoblasts. The mouth and tongue were not affected, but the abdominal symptoms were severe. Four weeks after admission to hospital a lobar pneumonia of the lower lobe of the left lung set in and ran a critical course. When the pulmonary condition cleared up a rapid improvement in the abdominal symptoms ensued and the man made a complete recovery.

In another case (No. 107) lobar pneumonia supervened upon blood transfusion for a haemolytic crisis. We are inclined to attribute his final recovery from sprue to the reaction which followed upon this pneumonic attack.

The patient, aged 61, had been known to be suffering from sprue for at least six years. On admission to hospital on March 24, 1926, he was comatose with incontinence of urine and faeces and did not regain consciousness for fourteen days. The blood count at this time was as follows : r.b.c. 1,100,000, haemoglobin 30 per cent., leucocytes 2,000. An extreme degree of poikilocytosis was present, whilst normoblasts were comparatively numerous. Two transfusions of whole blood were given—on March 29, 550 c.c., and on April 9, 400 c.c. ; consciousness was regained on April 11, but convalescence was checked by an attack of right basal pneumonia with consolidation and pleurisy on May 7. The signs were typical, the sputum rusty, and the condition of the patient was critical in the extreme. After crisis had supervened recovery was rapid. By July 1926 the blood was fully restored to normal, the red cells numbering 5,100,000 per c.mm. and the haemoglobin 100 per cent. Since that time he has remained in perfect health and has not exhibited any return of sprue symptoms since.

Special Aspects of Sprue as Affecting the Female.

In the female, amenorrhoea is a very prominent symptom in sprue. This we believe has not been adequately recognized, and it does not bear any close relation to the development of the typical sprue anaemia. Taking the average age of onset of the menopause in European women in the tropics as 45 years, we have been able to analyse thirty-three cases under this age, in twenty-two of whom amenorrhoea was present in varying degrees—of these twenty-two no less than nine presented normal blood pictures, six had a secondary anaemia of slight degree (i.e. 4,000,000 r.b.c.'s per c.mm. and 80 per cent. haemoglobin), while the remaining seven were characterized by an anaemia of a more severe type (i.e. 3,000,000 r.b.c.'s per c.mm. and 65 per cent. haemoglobin). Amenorrhoea, therefore, constitutes an early clinical sign of sprue in the female.

The relationship between sprue and pregnancy is well illustrated by the following cases :

Case 24. Aged 38. Sprue symptoms developed immediately after abortion. Anaemia moderate.

Case 44. Aged 30. Sprue symptoms developed immediately after birth of child. Anaemia slight.

Case 54. Aged 20. Still-birth followed by an abortion two years later. Sprue relapse during each of two subsequent pregnancies. Anaemia slight. Wassermann test negative.

Case 71. Aged 37. Relapse during pregnancy, subsequent to first onset of sprue. Anaemia absent.

An Analysis of Special Symptoms and Signs of Sprue.

It is not our object to recite an account of the more familiar signs and symptoms of sprue, but there are certain points around which obscurity still reigns. Our investigations have convinced us of the soundness of Manson's original classification of sprue into : *Complete sprue,* i. e. those cases presenting all the cardinal signs of the disease ; and *Incomplete sprue,* i. e. those cases in whom, tongue and mouth symptoms being absent, intestinal symptoms predominate. To this we wish to add a third, as originally suggested (6) by one of us, in Ceylon, namely, *Tongue or Mouth sprue,* i. e. those cases in whom tongue and mouth symptoms are predominant, it may be for years, prior to the advent of the familiar abdominal symptoms.
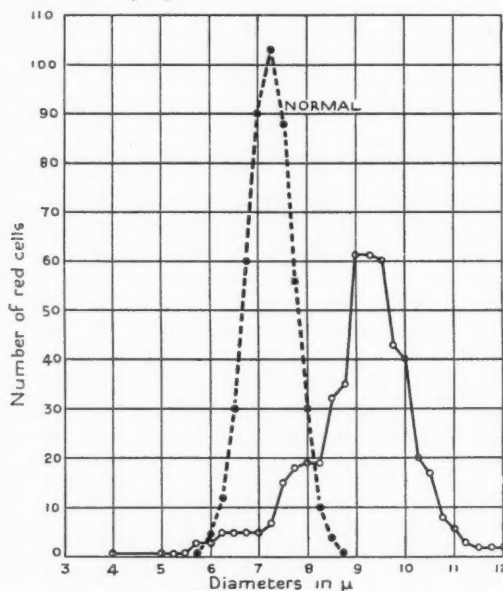
Price-Jones curve in the typical anaemia of sprue (see p. 423).

Tabulating our series by this classification we find that 22 per cent. of cases can be labelled as *Incomplete sprue,* while we have on record one undoubted instance falling into the third category.

TABLE IV.

Tongue Symptoms.

Completely absent in	44 cases	= 22 %
Tongue red	55 ,,	= 27·5 %
,, glazed	38 ,,	= 19 %
Aphthous ulceration	45 ,,	= 22·5 %

Mouth Symptoms.

Mouth sore in	25 cases	= 12·5 %
Aphthous ulceration	22 ,,	= 11 %

Oesophageal Pain.

Complained of in	25 cases	= 12·5 %

The stigmata of the sprue tongue are very variable. In the mildest cases they may only amount to undue sensitiveness of the buccal mucosa to hot fluids, spices, and tobacco smoke. In more advanced cases there is complete perversion of taste to salt and sweet foods; this is usually associated with anorexia and aversion to food of any kind. The fungiform papillae are usually distinct and hyperaemic, especially at the tip of the tongue. Salivation with dribbling of acid saliva from the mouth at night-time is an early, and often very distressing, concomitant. Aphthous ulceration of the buccal mucosa and of the tongue was present in 22·5 per cent. of the cases. In none were the aphthae more than 1–2 mm. 'in diameter. The aphthous ulceration appears to commence as a vesicle in the lower strata of the tongue epithelium which on bursting exudes a serous fluid and develops into a small ulcer. These aphthae, as is well known, are characterized by their evanescent character. They are extremely painful and sensitive, and have been seen on the inner margin of the lower lip, the fraenum linguae, the tip and sides of the tongue, the mucosa of the cheek opposite the lower molars, but never on the palate or the fauces. The polished appearance of the chronic sprue tongue is illustrated in Fig. 1.

Oesophageal pain was present in twenty-five cases. In no less than fifteen of these typical aphthous stomatitis was absent, so that it is not necessarily associated with the extension of the sprue process from the mouth. There probably exists, though it is difficult to prove, a sprue-like inflammation of the oesophageal mucosa akin to that seen in the mouth. This dysphagia is a very disagreeable symptom. The pain is variously described by sufferers as a painful contraction of the oesophagus on swallowing, even bland fluids, like milk, or the patient's own saliva. It may be referred to the xiphysternal cartilage or to a point in the centre of the manubrium. Oesophageal pain is almost invariably associated with flatulent dyspepsia, and this was absent only in two instances.

Aphthous stomatitis of a particularly acute and distinctive kind may attack the tongue and buccal mucosa, causing acute distress and inability to swallow anything but the blandest fluids, and may persist for nearly one year before the advent of gastro-intestinal symptoms. These cases appear to be rare and are particularly puzzling when first encountered. The condition somewhat resembles acute syphilitic stomatitis, and the exact diagnosis may remain in doubt for some considerable time. We may quote in detail the most typical instance which has come under our notice:

Case 197. Male, aged 55. This patient had resided in India and in China for many years. In August 1928 had severe attack of aphthous stomatitis with generalized glossitis, deep fissuring, and actual bleeding of the tongue. The process was so acute that the superficial epithelium of the tongue sloughed away in plaques and he could neither eat nor swallow. The process extended to the mucosa of the lips and the angles of the mouth were cracked. Salivation was excessive. On dietetic treatment the stomatitis cleared up temporarily, but relapsed in more acute form still in December of the same year, when it was associated with oesophageal pain and complete loss of taste. The response to dietetic treatment was remarkable, but he returned six weeks later with typical sprue diarrhoea and secondary anaemia, but on this occasion the mouth symptoms

were absent. There was no appreciable loss of weight. The Wassermann reaction was tested on three different occasions with a negative result.

The Abdominal Symptoms of Sprue.

The outstanding feature of sprue is the diarrhoea, which has certain characteristics, notably the large and copious stools, the pale or clayey colour, the amount of contained gas, the sour, nauseating, and penetrating odour. The precipitancy of the onset, accompanied by the passage of a large amount of flatus, together with the above characteristics, serves to differentiate it from other forms of diarrhoea. The patient is frequently wakened at night or in the early morning by the urgent desire to go to stool. Defaecation is accompanied by a sense of temporary relief and a feeling of exhaustion. Tenesmus, or straining at the end of the stool, may be present in only a small proportion of cases during the acute stage.

As noted originally by Manson, there are rare cases in which the stools bear all the sprue characters, but diarrhoea is absent. We have records of two such cases (see Table V).

A frequent characteristic of sprue diarrhoea is the passage of solid formed faeces, followed later by a diarrhoea of an explosive character.

The sense of scalding of the anal margin and the perianal skin by the passage of the acid motions is a frequent accompaniment in acute cases.

TABLE V.

Abdominal Symptoms.

(1) *Diarrhoea—Time of Day.*

(a) Early morning	69 cases = 34·5 %
(b) Any time	116 ,, = 58·0 %
(c) Morning and evening . . .	9 ,, = 4·5 %
(d) Night only	4 ,, = 2·0 %
(e) No diarrhoea throughout . .	1 case = 0·5 %
(f) Constipation and diarrhoea alternately	1 ,, = 0·5 %

In the subjoined Table VI we have tabulated the main abdominal signs of sprue. From this emerges the evident fact that flatulency, like the diarrhoea, is one of the chief abdominal signs of sprue, and was a noticeable feature in 72 per cent. of the cases. It is usually associated with intense meteorism.

TABLE VI.

(2) *Other Symptoms.*

(a) Abdominal pain	79 cases = 39·5 %
(b) Flatulency	144 ,, = 72·0 %
(c) Meteorism	101 ,, = 50·5 %
(d) Vomiting	27 ,, = 13·5 %
(e) Anorexia	18 ,, – 9·0 %

In our experience in early cases of sprue the meteorism is confined to the lower portion of the small intestine causing distension of the lower portion of the abdomen below the umbilicus (Fig. 2). It is only in the more advanced cases that the large intestine becomes involved, the inflation of the caecum and

ascending colon with gas being of such a degree as to be almost obvious on inspection. The observations on this point bear out what we believe to be true, namely, that the sprue process gradually extends downwards throughout the intestinal canal and may ultimately invade the rectal mucosa.

Contrary to what is commonly stated, vomiting may be an early feature in sprue. Acute vomiting may presage the onset of the diarrhoea, decreasing with the establishment of the more familiar features of the disease. In the later stages of sprue it is replaced by retching and a feeling of nausea. In acute cases vomiting may persist even on a milk dietary. In three cases he obtained a history of the acute onset of sprue with precipitant vomiting and diarrhoea resembling the onset of acute gastro-enteritis.

Shrinkage of the liver. Diminution of the liver dullness in sprue has been frequently noted by older observers as being almost pathognomonic of this disease. In our series an appreciable diminution of the liver was observed in 112 cases (56 per cent.), while in 87 cases the area was normal in extent, and in one case actual enlargement of the liver was noted, and he was found subsequently to be suffering from syphilitic hepatitis.

We are convinced, as the result of our observations, that the most marked shrinkage of the liver is found in those with the greatest wasting—that is, in the most advanced stages of the disease, and especially associated with aplastic anaemia of the Addisonian type. We suggest that the wasting of the liver in sprue may be specific, in so far that it may be connected with the non-absorption of fat through the intestinal mucosa, and it may be connected with dysfunction of the bone marrow and consequent production of sprue anaemia.

The cardinal signs of fully-developed sprue. The relationship in time of the mouth and tongue lesions to the fully-developed intestinal symptoms of sprue can be stated as follows. In the majority of instances (158 cases) the typical diarrhoea is first noted by the patient and may precede by even one year the advent of typical aphthous stomatitis, and then, as already stated, in 22 per cent. may never make their appearance at all. On the other hand, in 38 (or 19 per cent.) the stomatitis preceded the onset of the diarrhoea. In 2 per cent. of cases only did they coincide.

The Blood Picture in Sprue.

The blood picture has received attention from a great number of workers and has been summarized recently by N. H. Fairley, F. P. Mackie, and others (7), (8). These observers have stated that the pathological appearances of the bone marrow correspond closely with the types of anaemia as seen during life. Two types of anaemia are distinguished; the first characterized by hyperplasia, the second by complete exhaustion, or aplasia, of the bone marrow.

From a clinical viewpoint we also recognize two distinct forms of anaemia in sprue—the first, which is associated with the persistence of gastro-intestinal symptoms and appears to be dependent upon the absorption of some intestinal

toxin; the second, a true pernicious anaemia, which is due to exhaustion of the haematopoïetic system, and which may be a sequela of any active sprue process.
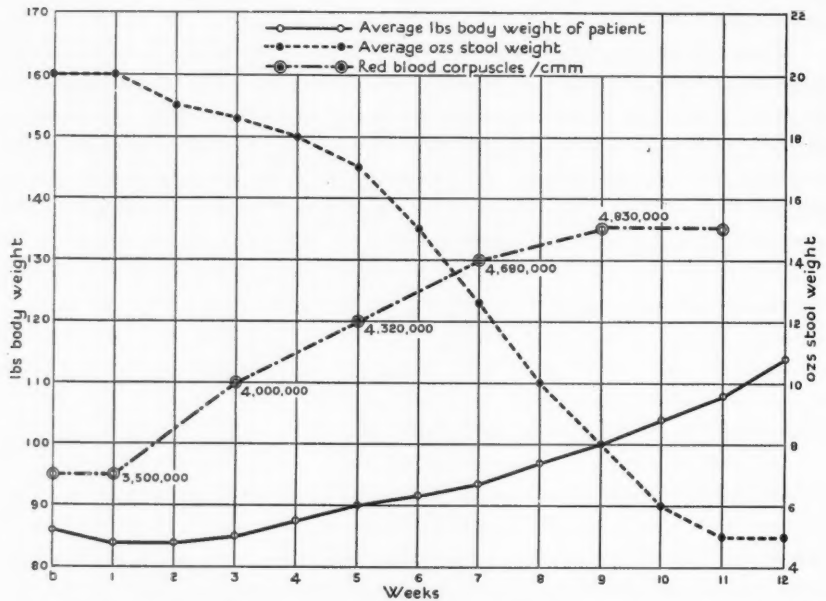
GRAPH I. A composite graph constructed from observations on ten cases, to show the relative increase in body-weight of patient and in red blood corpuscles per cubic millimetre with coincident decrease in average weight of stool over the same period of treatment.

All the cases of severe sprue anaemia occurred in patients in whom diarrhoea figured as the predominant symptom. Those with outstanding mouth or tongue symptoms all had blood counts of over 3,000,000 red cells per c.mm. and a haemoglobin percentage of 70.

This suggests strongly that the exhaustion of the bone marrow is brought about by continuous absorption of some specific intestinal toxin. Graph I constructed from a study of ten cases shows that when absorption has become re-established with progressive increase in body-weight and progressive decrease in size of stools the increase of red blood corpuscles runs an almost parallel course with that of the former.

The points to be noted from a study of 198 cases whose blood was investigated are as follows: In 53·5 per cent., or in well over half the number of cases, particularly in the early stages of the infection, the total blood count of red cells closely approached normality, but even this observation goes to show that morphological changes in the blood corpuscles are present, and thus points to hyperplasia of the bone marrow. In fifteen cases anisocytosis and poikilocytosis were noted in association with a red cell count of over 4,000,000 per c.mm. The colour-index is unity, or above 1·0 for the whole series. As noted by Fairley and his co-workers, normoblasts are but rarely seen, and are

recorded in only four cases in this series, i. e. in 2 per cent. The Price-Jones curve in the acute anaemia of sprue does not differ from that of true Addisonian anaemia (see graph attached).

In uncomplicated sprue cases our figures show that the leucocytes are well within the normal, or even below the normal, figure. A leucopenia, below 4,000 white cells per c.mm., was only noted in five cases ($2\frac{1}{2}$ per cent.), and this in association with extreme anaemia. In one case, in a haemolytic crisis, the white cell count fell as low as 2,000. In nine cases ($4\frac{1}{2}$ per cent.) there was an actual increase of the total leucocytes above 10,000. In seven of these no complicating factor was present to account for this rise in the leucocytes. In one with 24,000 leucocytes there was a *Bacillus coli* infection of the urinary tract. In the second a septicaemia was present.

A study of the differential blood count does not point to any factor of outstanding importance.

Patchy Pigmentation.

Pigmentation of the skin, usually of the face or of the abdomen, occurs in cases of the severe anaemia of sprue as originally noted in Ceylon by one of us (P. H. M.-B., Report, p. 34). This pigmentation disappears as the blood condition improves under treatment (Fig. 3).

Muscular Cramps and Tetany.

It is hardly possible to give the frequency of cramps as a concomitant of sprue symptoms. They are present in some form or other in almost every well-marked case associated usually with profound wasting and anaemia. These cramps are noted usually in the calf and thigh muscles when the patient remains long in one position as in sleep. In the early stages, and especially when diarrhoea is present, they may be extremely painful and troublesome, but they pass off directly the diarrhoea ceases, the patient begins to put on weight, and the blood condition begins to improve.

Tetany of the hands and feet have been noted in three instances in association with a predisposition to cramps. The hands assume the obstetric position in spasmodic contraction. The deep reflexes are increased and Chvostek's sign can usually be elicited on striking the angle of the jaw. This phenomenon, as well as cramps in sprue, is probably occasioned, as Scott pointed out in his original paper (9), by a calcium deficiency, or disordered calcium regulation. The cases in which it has been seen were those of sprue anaemia with considerable oedema of the legs and ankles. As in the case of cramps, this soon passes off as the general condition of the patient improves.

Observations on the Blood-pressure in Sprue.

Systematic observations on blood-pressure in well-marked cases of sprue were made in sixty-six cases, the average age of the patients being 49 years.

The method employed has been with the Tycos sphygmomanometer and goes to show that the systolic blood-pressure is about 20 mm. below the normal figure with a pulse-pressure of 40 mm. The blood-pressure is, of course, lower in the advanced than in the early stages of the disease.

The Sigmoidoscopic Appearances of the Bowel in Sprue.

For many reasons, especially on account of the debilitated condition of most of the patients on admission to hospital, it has not been possible to perform routine sigmoidoscopic examinations of the rectum and sigmoid. But enough has been learned from a study of eight cases to deduce the following.

No ulceration has been seen. In the acute stages with profuse diarrhoea the mucous membrane is injected and has a bright rosy pink appearance with complete absence of mucus and loss of the normal polished lustre of a healthy mucosa; in the chronic stages the bowel wall is attenuated and the mucous membrane is lax and of a pale greyish colour, and has a distinctly lustreless and atrophic appearance. As a general rule, the peculiar white or clayey character of the contained faeces can be recognized in the lumen of the bowel.

The Pancreas.

The diastatic reaction of the urine was tested in order to ascertain whether any involvement of the pancreas could be ascertained to exist by these means. The figures obtained were from 20 to 29 units, which is well within the normal limits, and in this manner sprue can be differentiated from acute and chronic pancreatitis whenever this difficulty should arise.

We are indebted to Dr. P. H. Martin for making a study by the dry method of the fat analysis of the stools of sprue in twelve of our cases fed upon a milk dietary. Our figures, as may be expected, show very considerable variation. The average total fat content is much higher than the normal, and is 46 per cent.—the extremes are 27 and 72 per cent. respectively. As has been frequently noted, the fatty acids predominate over the neutral fats in the ratio of 4 : 1.

As will be noted later, we are of the opinion that it is difficult to account for the large proportion of fat in the stools by the amount of fat which is ingested with the food, when the total bulk of the stool is considered. Cammidge (10) records much the same figures, and attributes the excess of fat in the faeces to defective absorptive power of the intestine.[2]

On the other hand, it may be, as Sokhey and Malandkar (11) have pointed out, that other factors may be involved, for these observers, by employing Saxon's wet method of fat analysis of faeces, have obtained figures in agreement

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[2] The normal fat content of dried faeces is 20–25 per cent. and the neutral fats and fatty acids are present in equal amounts. In pancreatic disease the total fat in the faeces totals 70–80 per cent. with an abnormal relative percentage of neutral fats (Tidy, H., *Synopsis of Medicine*, 1924, pp. 414–84).

with those given above, but as all these cases were fed on a milk dietary they were compared with an equal number of bed cases on milk and suffering from other diseases. The results obtained ranged from 29·7 to 73·6 per cent. of fat, agreeing closely with the figures obtained in sprue.

Radiographic Examination of the Digestive Tract in Sprue.

We are indebted to Dr. J. Duncan White for his reports on the X-ray examination of the small and large intestine in three cases of acute and three cases of chronic sprue. Unfortunately notable distinctive features are lacking. In the acute cases the opaque meal is hurried through the small intestine, and at the end of six hours is massed in the ileum. The terminal coils of the ileum are greatly dilated. In the chronic cases the large bowel was investigated by means of an opaque enema. The lumen of the bowel is distended while the outline of the transverse colon is 'smoother' than the normal bowel, and marked haustellation is lacking. These appearances are exactly what would be expected from a bowel subjected to chronic inflammation.

Observations on Pyrexia in Sprue.

There is overwhelming evidence that in the majority of instances the sprue process from the commencement to even a fatal termination runs an apyrexial course. Cases of continuous pyrexia due to the sprue syndrome, in the absence of other complicating factors, are rare. That they do occur, and that in these cases they are associated with anaemia of pronounced degree of the aplastic type and are apparently dependent upon absorption from the bowel, can be seen from a study of the accompanying chart. Here the temperature fell, and a general improvement in the patient's condition and in the blood-picture coincided accurately with the introduction of a rigid sprue dietary. In this series the concurrence of pyrexia has been noted four times.

Case 40. Mrs. C., aged 43. Was first seen in March 1922. Symptoms commenced in Kasauli in India with attacks of what was called 'hill diarrhoea'. On arrival in England the sore tongue, aphthae, and diarrhoea occasioned the correct diagnosis of sprue. On milk dietary and general measures she improved to a very great extent and remained well for nearly four years. In December 1925 she had an acute relapse which on account of its association with pyrexia was not considered by her medical attendant to be sprue. In April 1926 an acute haemolytic anaemia developed with a colour-index of 1·6—haemoglobin percentage of 27, a leucopenia of 2,000, and red blood count of 820,000. The effect of suitable sprue dietary in reducing the pyrexia and in generally improving the patient's condition was dramatic. Three months later the blood condition had greatly improved and the patient was leading an active life. (See Temperature Chart on p. 426.)

Emaciation.

It is a matter of common knowledge that the emaciation of sprue exceeds that of almost any other disease. In appearance this emaciation resembles that

of chronic starvation (Figs. 5, 6) and is so extreme that the patient may have
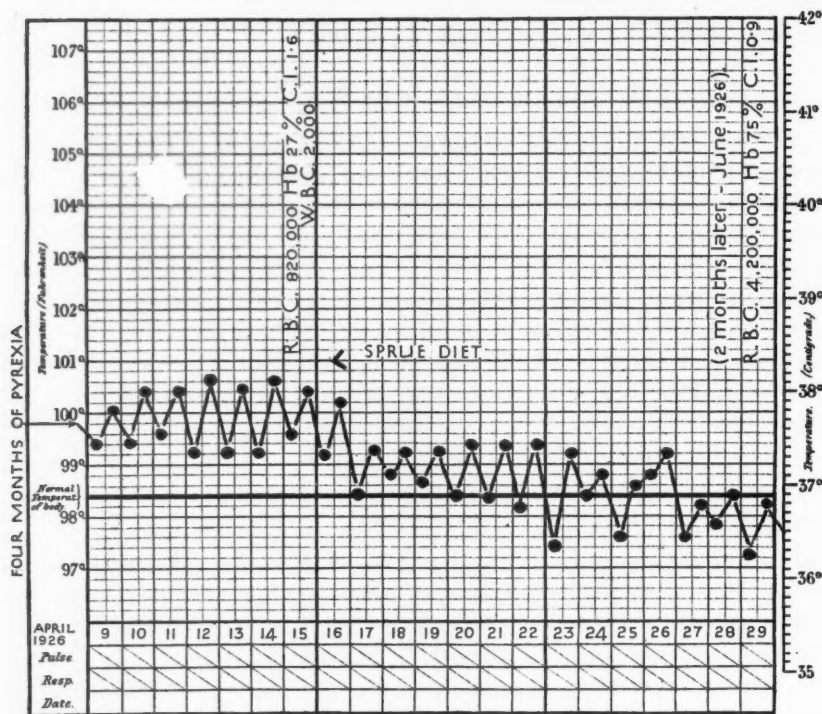lost almost half his body-weight, as in the accompanying illustration.

FIG. 4.   Temperature chart of Case 40, showing reaction to dietetic treatment.

Treatment.

The more the management is conducted in detail the more difficult it becomes
to lay down rules. 'What is one man's meat is another man's poison' was
never better exemplified than in sprue. Of one thing we are quite certain, that
the *sheet anchor* in the treatment of sprue is diet—to this all medicinal treatments
are subsidiary. We are still far from elaborating a drug which is specific for the
intestinal symptoms of sprue.   Many have been put forward from time to time,
and we have endeavoured to give them all a fair trial and to assess impartially
any specific values that they may possess.   At the same time it is necessary at
the outset to admit of a distinct individual and psychological factor in the
treatment of this disease. The individual idiosyncrasies of patients of the intelli-
gent and impressionable type, such as constitute the great majority of our
patients, are never more strongly exemplified than when dealing with different
articles of diet. Individual patients thrive on the most widely diverse diets, but
we submit that a strict milk dietary in sprue is not necessary. Some individuals
have an intolerance of, if not an incapacity to digest, milk.

With this proviso, that we have varied our diet to the needs and preferences of the individual, we are of the opinion that the two principal ingredients of a mixed dietary, namely, fats and starches, are incapable of complete digestion in the initial and acute stages of sprue. The indications are, therefore, to introduce as much easily assimilable and non-irritating protein as the patient is capable of absorbing.

The problem of diet in sprue is really one of restoring the balance of absorption. This is well seen by a study of the graphs which we have drawn up to illustrate the principles on which sprue treatment should be based.

Case 100. Female, aged 44 (*illustrating methods of compiling Graphs III, IV, V*).

Observed for 9 weeks. Total increase in body-weight, 27 lb.

Week	Diet.	Intake.		Output.		Weight of Patient
		Solids.	Fluids.	Faeces.	Urine.	
		oz.	oz.	oz.	oz.	lb.
1st	Milk ℥ 46, liver soup ℥ 8, rusks ℥ i	19	420	48	316	79
2nd	Milk, &c. + egg, banana, sago	84	504	64	525	79
3rd	Milk, &c. + 2 eggs, banana, sago	136	528	65	543	85
4th	,, ,,	157	560	104	469	89
5th	,, ,,	161	560	87	522	93
6th	,, ,,	180	560	79	490	96
7th	,, ,,	163	574	205	552	100
8th	,, ,,	177	626	88	562	102
9th	,, ,,	206	630	52	621	106

Case 96. Female, aged 43.

Observed for 10 weeks. Total increase in body-weight, 28 lb.

Week.	Diet.	Intake.		Output.		Weight of Patient.
		Solids.	Fluids.	Faeces.	Urine.	
		oz.	oz.	oz.	oz.	lb.
1st	Same as in Case 100	22	506	47	369	87
2nd	,, ,,	51	575	36	373	86
3rd	,, ,,	88	542	29	410	88
4th	,, ,,	135	556	34	463	90
5th	,, ,,	161	586	47	552	92
6th	,, ,,	157	608	53	567	94
7th	,, ,,	153	658	56	414	96
8th	,, ,,	167	684	51	624	97
9th	,, ,,	170	680	70	603	100
10th	,, ,,	161	668	68	648	101

Case 102. Male, aged 47.

Observed for 6 weeks. Total increase in weight, 16 lb.

Week.	Diet.	Intake.		Output.		Weight of Patient.
		Solids.	Fluids.	Faeces.	Urine.	
		oz.	oz.	oz.	oz.	lb.
1st	Same as in Case 96	43	612	68	417	131
2nd	,, ,,	90	658	43	626	133
3rd	,, ,,	146	619	69	572	137
4th	,, ,,	212	616	82	517	139
5th	,, ,,	210	614	69	494	144
6th	,, ,,	202	563	80	391	147

We have studied the variations in the weight of an average case when placed in bed and fed upon this simple diet. This shows (Graph II) that there is an actual loss of body-weight, amounting to almost 5 lb. during the first two weeks of dietetic treatment on a mixed milk and protein diet, and is probably due to loss of retained tissue fluids. After this fall has been properly established, a gradual increase of body-weight commences.
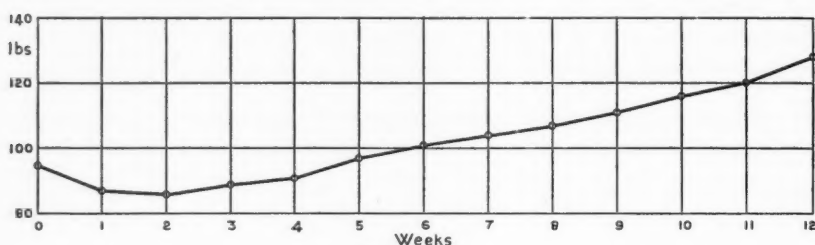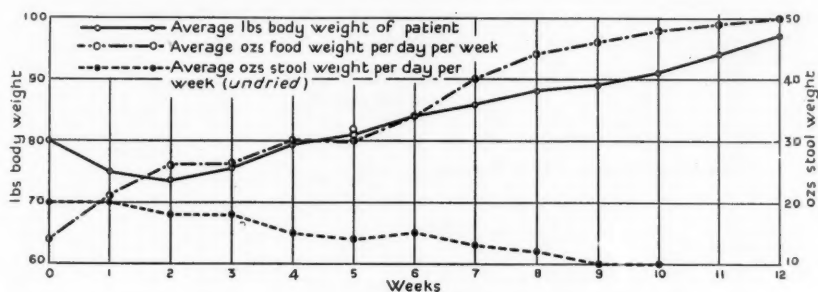

GRAPH II.
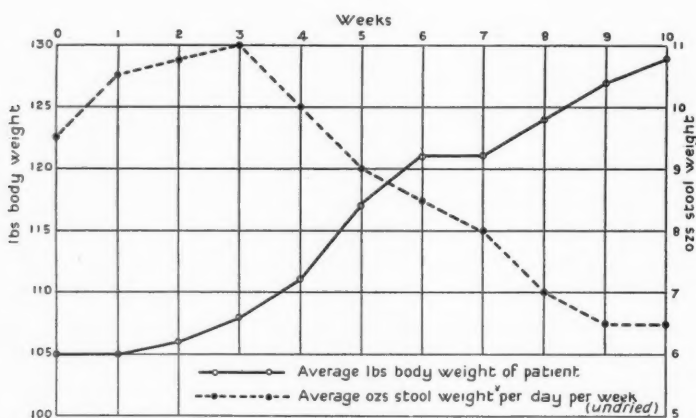
GRAPH III.

Furthermore, we are able to show in Graph III (average of ten cases), that a definite decrease in the amount and weight of the stool (gross weight with contained fluid, undried) runs parallel to the increase of body-weight. In other words, the replacement of loss of body-weight is inversely proportional to the amount of excreted material.

To estimate accurately the intake of solid and liquid food and to calculate the output is a physiological problem, and one which would entail a far more detailed study in metabolism than we have been able to make. The rough estimates, however, have a definite clinical value and may constitute the basis for finer metabolic studies on similar lines.

Graph IV illustrates the principles that obtained in Graph III, with the addition of an attempt to estimate the intake of solid nutriment, as opposed to liquid, and its effect upon the gross weight of the stool. It will be seen that the

increase in food intake runs parallel with the increase of the patient's body-weight, and inversely with the amount of faeces excreted, when once the absorptive power of the intestinal mucosa has been readjusted. The tables which accompany the graph give the actual figures in five selected cases in whom an appreciable increase in body-weight could be recorded.

GRAPH IV.
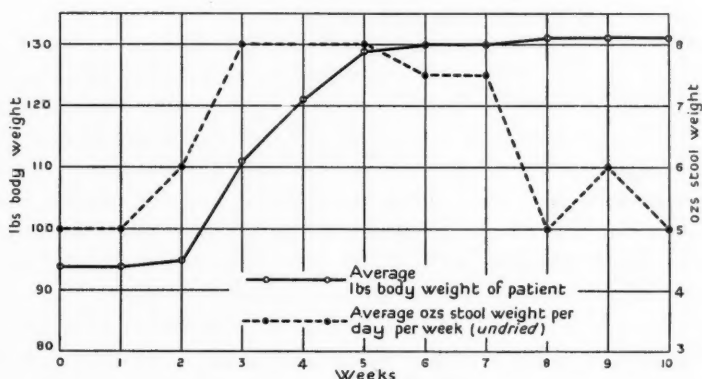
GRAPH V.

That the rise in body-weight in sprue is as rapid as it is striking is shown by a study of Graph V, where an increase of body-weight of 37 lb. is recorded in ten weeks. It is the suddenness of the rise of the curve to which we would like to draw attention, and we doubt whether it can be paralleled in the study of any other disease (Figs. 7 and 8). Another point is the large size of the stool in these favourable cases. As the intake of solid food and assimilation progresses, so the weight of the stool increases up to a certain point (in these cases for nearly three weeks). Therefore, from a clinical point of view, the actual size and weight of the stool should not be taken as an indication for restriction in the patient's diet, especially when associated with progressive increase of body-weight, as has been the common teaching heretofore.

Dietetics. No cases in this series have been treated for more than one consecutive week on milk alone. It is not necessary to specify any more on

the subject than to set forth, as is done in the accompanying Table VII, the dietetic ingredients used in the different stages of the disease with the approximate calorie values. We have employed a mixed milk and protein dietary.

TABLE VII. *Dietary and Food Values.*

DIET I.

First Week.

Milk. Three pints daily in 5 oz. feeds given at two-hourly intervals.

Protein	60 grm.	= 246 calories	
Fat	60 ,,	= 558	,,
Carbohydrate	86 ,,	= 352	,,

Total calorific value = 1156 calories.

DIET II.

Second Week.

Milk. Three pints daily as in Diet I.
   In addition, sago 3 oz. twice daily.

Sago 6 oz. contains 17 grm. of carbohydrate with calorific value = 69 calories.

Liver Soup is added, 12 oz. in the day, containing approximately

16 grm. of carbohydrate	}	= 691 calories.
80 ,, protein		
32 ,, fat		

Total calorific value = 1916 calories.

DIET III.

Convalescent Diet.

  Breakfast.

Porridge.		Carbohydrate.	Protein.	Fat.	Calories.
Quaker oats	¾ oz.	0·5	0	0	2
Milk	¼ pint	7	5	5	95
Sugar	½ oz.	15	0	0	61
					158

1 Egg lightly boiled. Protein 6, Fat 5·5 = 50 calories.
   or *Boiled Fish*, 3 oz. = 61 calories.
      (Haddock, plaice, turbot, cod, sole, or whiting.)
Toast, 1½ oz. Protein 3, Carbohydrate 30 = 135 calories.
Tea (very weak), of no food value.

Approx. total calorific value = 350 calories.

11 a.m. ½ pint of warm milk = 192 calories.

Lunch.		Carbohydrate.	Protein.	Fat.	Calories.
Liver Soup	12 oz.	16	80	32	691
Boiled Fish	6 ,,	0	30	0	123
Chicken	4 ,,	0	30	9	206
or Rabbit	4 ,,	0	40	8	238
Mashed Potato	2 ,,	12	15	0	110
Spinach	3 ,,	2·5	2	0	18
or Veg. Marrow	3½ oz.	5	0	0	20
or Peas	1½ ,,	5	3	1	42
or Cauliflower	4 ,,	2	1	0	11
Milk Pudding	½ pint	14	10	10	192
Baked Apple	6 oz.	45	0	0	184
or Banana	3 ,,	60	0	0	246

Approx. total calorific value—Average 2080

TABLE VII (*continued*).

Tea.

    Toast, 3 oz. = 270 calories.

    Madeira
        or Sponge Cake } 3 oz. = 314 calories.
        or Biscuits

    Weak Tea, of no food value.

    Total calorific value = 584 calories.

Dinner		Carbohydrate.	Protein.	Fat.	Calories.
Brain	4 oz.	0	10	11	143·3
or Sweetbread	3 ,,	0	15	1·6	75
Calves-foot Jelly	3 ,,	15	3	0	74
Banana	3 ,,	60	0	0	246
Arrowroot	½ pint	12	5	5	116

Average total calorific value = 550 calories.

Average daily calorific value :

Breakfast	.	.	.	350	calories
11 a.m.	.	.	.	192	,,
Lunch	.	.	.	2080	,,
Tea	.	.	.	584	,,
Dinner	.	.	.	550	,,
			Total	3756	,,

Diet No. 1 is given during the first week. It is admittedly of a low calorie value with the patient prone in bed and carefully nursed. Diet No. 2 is given from the second week onwards and is of a higher protein value than the first. Diet No. 3, of a distinctly high calorie value, is instituted from the third week onwards and during convalescence according to the special needs of each particular patient. We have found in practice that this diet must be persisted in for six months or more during convalescence till the stools have become of normal size (i. e. 6 oz. daily) and proper faecal consistency and colour. We have found that this departure from the rigid milk diet of a previous decade has been of very distinct advantage to the patient both from a metabolic and from a *psychological* point of view. The variations from a monotonous diet, and release from a still more monotonous life, we regard as of paramount importance in the treatment of this disease. This is well borne out in the fact that the patients in our series thus treated did not manifest signs of marked mental irritation, which is so typical in sprue patients under other circumstances.

The main departure from these standardized diets has been the introduction in certain cases of shredded raw meat in the form of raw meat sandwich up to 8 oz. per diem. *Recipe* as follows :

Raw meat sandwich—Take ¼ lb. of best beefsteak, free from fat. Cut small and pass through fine mincer. Toast two thin slices of bread slowly so that it is dry right through. Add a small quantity of pepper and salt to the mincemeat and spread between the toast.

The indication in the institution of the meat dietary may be taken as follows : The patients were over 45 years of age ; they were intolerant to large quantities of milk (i. e. over 60 oz. per diem), and especially were these associated with pronounced anaemia.

The results of the meat treatment, when palatable to the patient and assimilated by him, were most favourable, and the good effects were shown in the diminution in flatulency, the increase of body-weight, and the material improvement in the blood count. (Graph I.) The statistics which have emerged from a study of our figures place the meat protein dietary of sprue in a favourable light. We have given it to forty-five cases, in all of whom clinical results were good, and on the whole the bulk of the stool passed is certainly less than in similar cases fed mainly on a milk dietary.

In those to whom a raw meat dietary is repugnant we have found that lightly-steamed meat with the addition of gravy may be substituted. The meat should be steamed in the following manner :

Shredded tender undercut of beef 4 ounces. Steam with 6 ounces of water for 5–7 mins. Add pinch of salt. Serve as sort of thick soup with lemon juice, or slice of tomato.

Recipe for liver soup. Simmer gently $\frac{3}{4}$ lb. of minced calves liver in 25 ounces of water for two hours : strain, add one teaspoonful of marmite and a small amount of pepper and salt.

Liver soups and liver extracts. Liver soup made as above has been given as a routine to every case in this series. This practice is of long standing and dates back to the days of the late Sir Patrick Manson, who first employed it in Hong Kong in 1883. It has always been found, when made according to the accompanying formula, to be well assimilated and tolerated in sprue. Its most favourable effects are seen in those cases with the most pronounced degree of anaemia. This was a clinical observation which was well substantiated before the introduction of a specific liver dietary in Addisonian anaemia by Minot and Murphy. We are of the opinion that liver and liver extracts are indicated in sprue and react upon the haematopoïetic system in the same manner as in Addisonian anaemia, as has been described minutely by Rabe (12), Ashford (13), (14).

We regard liver treatment as an essential accessory to the main principles of dietetics in sprue. In our series not one single case was intolerant. Latterly, considering the addition of vitamin extracts to be advisable, we have employed marmite $\frac{1}{4}$ teaspoonful or less to every 8 ounces of liver soup. Liver extracts such as those of Eli Lilly may be added to every 8 ounces of liver soup to increase the concentration.

The disadvantages of an unbalanced dietary have never been sufficiently emphasized in sprue, and to excessive sterilized milk dietary we attribute the scorbutic-like stigmata such as the petectual haemorrhages on the arms and hands and the liability to bruising often seen in advanced cases of sprue. Actually one acute case of scurvy with purpuric haemorrhages into the skin developed in a patient who had been fed on board ship for four weeks on pure conserved milk. All the scurvy symptoms disappeared dramatically on the introduction of orange juice followed by those of sprue.

Fruit and vegetables in the treatment of sprue. Fresh fruit has up to the present held a premier place in the dietetic treatment of sprue. The strawberry

treatment has actually become a byword in medicine. By some it has been held that the fresh strawberry, or extracts of the same, exhibit an almost specific effect, so much so that resource to this luscious fruit has been made in the off season at exorbitant prices. We confess that we have been unable to obtain any evidence for this hypothesis. Fresh fruit, probably on account of its vitamin content, is undoubtedly of definite value, especially in those cases where constipation after rest in bed or a bland diet takes the place of obstinate diarrhoea. In the summer season, when strawberries are naturally ripened, we find that in moderate amounts of $\frac{1}{2}$-1 lb. a day they fulfil the purpose of a natural laxative. At other seasons of the year we find that the addition of one over-ripe Canary banana is almost equally efficacious, and whenever the condition of the tongue and mouth permit, the addition of the juice of one orange a day fulfils much the same purpose. We do not admit the specific value of any one form of fruit. Possibly the fresh bael fruit as employed in the East acts beneficially in much the same manner, and it can now be obtained as paste in glass jars. Almost as efficacious is the raspberry, given in the same amounts when the strawberries are out of season, and we have seen good effects following the ingestion of blackberries and fresh blackberry jelly. A baked apple is a very useful adjunct to the dietary and so are stewed prunes. In severe cases of constipation we have used boiled onions, spinach, and vegetable marrow with success. In the winter season fresh sliced tomatoes given with the meat dietary have proved useful and are palatable.

Other ingredients in the diet. A lightly-boiled or poached egg can always be given with safety, even to acute cases, directly the diarrhoea shows signs of diminishing; the same may be said of milk jellies (such as Chivers'), junket, calves-foot jelly, Valentine's meat extract, sago in small quantities, arrowroot, and blancmange. There are some instances in which whole milk is not tolerated when peptonized milk or Benger's preparation, Almata (a proprietary article), bovril and milk (the addition of one teaspoonful to every half-pint of milk), and even sour milk (or yoghourt) are useful in stimulating the appetite of the patient. One golden rule emerges, namely, that no considerable additions to the dietary should be made unless the patient exhibits a desire for food; and it has been our experience that a ravenous appetite invariably preludes an increase in weight in a patient who is obviously improving under treatment.

The addition of boiled or steamed fish and roast chicken should be deferred until such time as the patient is able to digest more solid articles without the production of indigestion or flatulency. The latter we regard as a most significant sign of tolerance to any particular article of dietary. We confess that we have not great faith in a prolonged fish dietary; it is monotonous, and often in our opinion less beneficial than raw meat or stewed chicken, and, as has already been emphasized, the psychological or human factor is an all-important one.

The introduction of solid cereal dietary sometimes presents difficulties. The patient longs for something solid into which he may set his teeth. Therefore rusks (McVitie and Price's digestive rusks), baked bread, or toast in thin

slices should be given as soon as they masticate with ease. An agreeable form of rusk and the one most easily tolerated by the patient is a sweet rusk known as ' Verkade's Ronde Beschuit ', obtainable from Fortnum and Mason and other well-known dealers. In extreme cases of intolerance to carbohydrates and those cases exhibiting a progressive degree of intestinal atrophy we have found such simplified food as Energen Bread extremely useful. In any case, whatever form of rusk or cereal is used, from 1–2 oz. of such per diem is sufficient; on the other hand, we find gross carbohydrates, such as whole wheat or brown bread and potatoes, are badly tolerated and increase the flatulency.

Care of the Mouth and Tongue.

It is a curious fact, which has already been commented upon by many observers of sprue, that the tongue and mouth symptoms are aggravated in an inverse ratio to that of the diarrhoea. Rarely both are exacerbated at the same moment. Therefore the most evident and distressing aphthous ulceration with a sensitiveness of the buccal mucosa becomes evident when the diarrhoea is quiescent. This is one of the most distressing features of sprue, and one in which it is most difficult to explain its true portent to one's patient. We are convinced that the obvious measures are extreme cleanliness, using bland mouth-wash, such as potassium chlorate or glycerine and borax, after each meal. For the aphthae themselves there does not appear to be any specific treatment. By nature they are very evanescent, but the application of the silver stick seems to hasten their disappearance. We may add that the mouth symptoms may persist for a considerable time after the bowel has become regulated and where the other more active symptoms of sprue have disappeared.

The sprue process appears to burn itself out, and the appearance of mouth symptoms does not by any means indicate that a relapse of the full sprue picture is imminent.

However, it is a useful clinical guide to consider a patient with obvious tenderness of the mucosa of the mouth and with unrestored function of the filiform and fungiform papillae as incompletely restored to health. We consider it of great importance that, directly the condition of the mouth permits, any grossly septic teeth should be extracted by *gradual* stages. On the other hand a too precipitant extraction of a large number of teeth with liberation of streptococcal toxins in the mouth may bring on an acute relapse.

The tongue and mouth should constitute an index of what is going on in the rest of the alimentary tract.

Aperients.

As obstinate constipation and balling of faeces is almost the invariable rule at some period of the disease the choice of a suitable aperient is important. The more potent aperients, such as colocynth, calomel, and the salines are contra-

indicated in view of the delicate state of the intestinal mucosa. We have found the agar preparations of liquid paraffin most satisfactory when given in doses of 1–2 drachms at night. Phenol-phthalein and liquid paraffin has proved advantageous. In more obstinate cases there is nothing better than nightly doses of one teaspoonful of castor oil. A mild aloes pill may sometimes be used with advantage. Sometimes an enema of 8 ounces of olive oil becomes necessary or even a glycerine suppository. Gentle massage to the abdomen is also an accessory.

Drugs.

The use of drugs in sprue is singularly limited. For checking the diarrhoea there is nothing better in our opinion than Batavia Powder (*Pulv. Bataviae Co.*). This is a modification of the well-known Peter Sys' Specific of Shanghai which has been mentioned by Manson, Cantlie, and other observers.

Batavia Powder appears to be powdered cuttle-fish bone, coloured with an iron compound, probably ferric oxide. Peter Sys' powder is identical with the omission of the iron and the addition of essential oil of peppermint. The powder is given suspended in milk or water in the dose of one teaspoonful a day; it may even be given in obstinate cases of diarrhoea up to 3 drachms daily. In some cases of diarrhoea during convalesence it is advantageous to give it in wafer cachets of gr. xv each four times daily.

In diarrhoea of a less obstinate character Crooke's collosal kaolin in doses of 1 drachm daily answers much the same purpose, while on occasion a bismuth and magnesia mixture (bis. oxycarb. gr. xv, mag. carb. pond. gr. xv) with chloroform water is useful in checking the flatulent dyspepsia.

In cases where the gastric symptoms are due to a relative achlorhydria we have recently found that the exhibition of dilute hydrochloric acid min. xx in orange juice after each feed of very distinct benefit. In our experience it does not increase the tendency to diarrhoea.

The best method in our opinion of combating flatulence is the provision of a satisfactory and easily assimilable diet suitable to the particular needs of each individual patient. There are other subsidiary methods. The first we consider is the exhibition of small doses of castor oil, one teaspoonful at night; next the injection of small doses of pituitary extract, ½–1 c.c.—both of which have been found to expel the flatus in extreme cases of meteorism. But probably the most convenient method is to give the pituitary extract in tablet form, such as Kinazyme tablets put up by Carnrick's and given in a dose of one tablet three times daily. The immersion of the patient in a hot bath, the application of stupes to the abdomen, and the insertion of a flatus tube into the rectum have from time to time been resorted to. Salol. gr. x in cachets three times daily is sometimes efficacious.

Since Scott's (15) publication on this subject from 1923 onwards, a trial has been made of the combined treatment of calcium lactate in cachets, gr. x three times daily, with extract of parathyroid (Parke, Davis & Co.), gr. 1/10th

twice daily, in 137 cases in this series. We confess to a considerable amount of diffidence in pronouncing a final verdict on this method of treatment, which has been given a very considerable degree of prominence, on which so many favourable reports have been based. It is almost impossible in a disease where dietary, as is admitted on all sides, plays such an important part, to assess the exact value of any new drug treatment.

We confess that we have not observed any marked specific effect of this treatment. We have endeavoured to trace the liability to relapse after intensive treatment with parathyroid and calcium for six weeks or more, and we have at least four specific instances where more than one relapse of acute symptoms occurred. In one instance (Case 88) it did not prevent a fatal issue to the disease, and we have had experience of some six cases where clinical improvement took place immediately the calcium lactate and parathyroid *ceased* to be given. We have been unable to trace accurately the calcium content of the blood of all the cases under review—this has already been done by other observers, notably Mackie and Fairley—but we have endeavoured to assess impartially any therapeutic value we could discover from this combination. In some cases we have found that the exhibition of calcium lactate diminishes the flatulency. At any rate we can say we have seen no deleterious effects attributable to this form of treatment, and we maintain that wherever it appears to have a favourable effect it should be persisted in.

Yellow santonin dissolved in olive oil, as originally advocated by Begg, has been given a limited trial, gr. iii to gr. v daily. We have observed no specific effect in four cases, and therefore this treatment has been abandoned.

For the anaemia of sprue, and especially the secondary anaemia which accompanies the intestinal symptoms (see p. 422), the deep subcutaneous or intramuscular injection of arsenate of iron (Fraisses' ferruginous serum) twice to three times weekly appeared to be efficacious, but if given in excessive doses appears to provoke diarrhoea.

Liquor arsenicalis (Fowler's Solution) up to 15 minims daily in graduated doses shows similar results and is best given in combination with blood transfusion.

Blood transfusion. We have already reported upon the dramatic effects of blood transfusion in extreme cases of sprue anaemia. The results have already been published (16), and there is therefore no need to elaborate it still further. Blood transfusion to our mind is indicated in those cases who do not respond satisfactorily to liver extracts and a continued milk and protein dietary. The amount need not necessarily be large: it seems to exert a stimulating effect upon the bone marrow, and, what is more satisfactory to observe, the results when watched over a period of three years appear to be permanent and to result in the disappearance of the more active intestinal manifestations of sprue. A table is appended. (Table VIII.)

TABLE VIII.

Case No.	Amount transfused.	Before		After	
		R. B. C.	Hb.	R. B. C.	Hb.
	c.c.		%		%
136	70	2,670,000	70	3,840,000	80
163	150	1,900,000	40	4,200,000	80
172	70	3,410,000	75	5,300,000	95
178	200	3,000,000	75	4,890,000	85
181	500	3,580,000	70	4,800,000	85
187	200	3,610,000	75	4,780,000	85
188	100	4,200,000	80	4,680.000	85
199	280	1,440,000	46	4,600,000	80

The corpuscles of the donor were matched in all cases against the serum of the recipient, in addition to grouping. The blood of the donor was citrated before injection.

Heliotherapy.

Certain cases do not respond readily to dietetic treatment, and in these exposure to the direct rays of the sun, as in sun-bathing or even the application of ultra-violet rays to the chest and abdomen, acts as a most remarkable stimulant; and in our opinion heliotherapy holds most distinctly a place in the therapeutics of sprue.

Summary of Body-weight resulting from Treatment.

TABLE IX.

(1) Gain in weight was recorded in 146 cases of the series . . = 73 %
(2) Loss of weight was recorded in 32 cases of the series . . = 16 %
(3) Cases in hospital for less than two weeks, or who died, or who showed no change in weight between admission and discharge, 22 cases of the series . . . . . . = 11 %

    (a) Average increase in weight per patient . . . 9½ lb.
    (b)   ,,   ,,   ,,   ,,   per week . . . 1½ lb.
    (c) Average loss in weight per patient . . . . 2¼ lb. in 32 cases

Differential Diagnosis.

To those who are intimately acquainted with sprue the clinical aspect of the disease bears such a distinctive character that the differential diagnosis is seldom called into question. Some cases of *chronic pancreatitis* bear a superficial resemblance to sprue; we have, however, failed to experience any great difficulty in differentiation. The stools in chronic pancreatitis are, it is true, massive and light coloured, and contain a large quantity of undigested fat, but this differs from that found in sprue stools in so far as it is separate from the solid material and not intimately intermingled as in the case of sprue. Then there is the diastatic reaction of the urine and other biochemical tests which are of use.

From true *Addisonian anaemia* the differentiation is by no means so easy. As has already been pointed out (17), the stomatitis of Addisonian anaemia can

be differentiated on clinical grounds, and the stools of pernicious anaemia do not, as a rule, bear the distinctive features of sprue, nor have we observed in any of our sprue cases any evidences of peripheral neuritis such as are frequently associated with pernicious anaemia. In the course of this inquiry we have encountered three cases in which the diagnosis between sprue and Addisonian anaemia has lain in doubt for a year or more and in which frequent haemolytic crises were accompanied by pyrexia and the appearance of liquid diarrhoeic stools of a sprue-like nature. However, in all three cases, sooner or later signs of peripheral neuritis in the shape of areas of anasthesia or of tingling or numbing sensation in the limbs has made its appearance.

From *Coeliac disease* (intestinal infantilism), or the Gee-Herter syndrome, the diagnosis has not seriously come into question in the cases under review. Hess Thaysen (18) has recently raised this question in Denmark and has sought to establish the existence of what he calls non-tropical sprue. For our part we do not hesitate to say that coeliac disease as it occurs in children, and sprue as it occurs in adults, are undoubtedly two separate entities. No case of a sprue-like disease in children hailing from the endemic area of sprue in the tropics has been observed. We regard this as a very cogent answer to the question, and it is more than probable, in our opinion, that the resemblance between these two diseases is only a superficial one. The sprue-syndrome is the result of a specific microbic infection of the alimentary tract, while coeliac disease is probably the result of a development defect in absorption, as is seen by the fact that capacity for fat absorption in the latter state is restored after puberty is passed. That the grosser clinical resemblances of these two diseases is somewhat similar does not by any means prove their identity. Thaysen would group sprue, non-tropical sprue, and Gee-Herter disease as idiopathic steatorrhoeas, in order to differentiate them from the pancreatogenous, alcholic, and possibly enterogenous fatty diarrhoea. According to this observer, the idiopathic steatorrhoeas, especially coeliac disease and non-tropical sprue, are characterized by a low blood-sugar curve.

We have never found any practical difficulty in differentiating tubercular disease of the small or of the large intestine from sprue. It is true that from time to time caseous tuberculosis of the mesenteric gland may give rise to emaciation, meteorism, and the passage of pultaceous light-coloured stools which resemble those of sprue; but cases of this description have not entered our medical horizon.

Our observations on aphthous stomatitis of streptococcal origin, and apparently intimately connected with streptococcal gingivitis, or pyorrhoea, go to show that the raw, red streptococcal tongue may be readily differentiated from sprue. In streptococcal stomatitis the buccal mucosa, the alveolar margins, the mucous membrane of the lips, palate, and fauces are attacked. Though they may be associated with a certain degree of ill health, they are not necessarily accompanied by any intestinal symptoms, anaemia, or loss of weight as in sprue.

It is said that in the advanced stages of this disease, sprue-like stools may be passed which, together with the stomatitis, has led various authorities to link pellagra and sprue together. Although there is no reason why sprue should not supervene in a case of pellagra, yet, on account of the associated pigmented skin lesions, we see no legitimate or satisfactory reason why these diseases should not be differentiated with ease.

It has happened on two occasions within the writers' experience that difficulty has arisen in the differential diagnosis between early cases of subacute combined degeneration of the spinal cord with high-grade anaemia and glossitic changes with gastro-intestinal symptoms in cases hailing from the tropics. Although these cases have responded rapidly, so far as the stomatitis and blood condition are concerned, to blood transfusion and a sprue dietary containing a high proportion of proteins, yet the development of a spastic paraplegia with sensory changes in the lower extremities has served to differentiate them from true cases of sprue. We venture to suggest that cases of sprue anaemia with neuritic changes which have from time to time been reported are referable to the category of subacute combined degeneration of the cord. We have never observed nervous changes in true sprue.

Period Necessary for Active Treatment.

In our series of cases the time spent in hospital for an average severe case of sprue is one of five weeks. We have provided definite evidence that with the improvement in the calorie value of the diet and the additions which have been specified the average time of treatment in hospital has been reduced on an average from seven to four weeks. These figures speak for themselves.

Table IX gives in detail the results in brief. It will be seen that in no less than 73 per cent. a very definite increase of weight could be recorded.

There is nothing we regret so much in this investigation as our inability to calculate the relapse rate. That there have been relapses after treatment we are perfectly willing to admit; but in only three instances of these 200 cases have the patients applied for readmission to hospital. There are many others whom we know are resident in this country and who maintain average good health. The greatest difficulty exists in following up those cases who return to the tropics and from whom no further news can be obtained. This must always obtain in any disease which occurs normally in the tropics and which is treated away from the country in which the patients normally live.

After-treatment and Care in Sprue Cases.

We can only state here in general terms the principles which we have learned, as the result of experience, to guide us in the after-care of sprue cases. They can be classified under the three headings of diet, climate, and exercise.

We have found it advisable for patients to adhere to the convalescent diet

referred to on p. 430 for at least six months after cessation of active treatment. This really means to say that the patient is able to partake of all reasonable articles of diet with the exception of coarse vegetables, such as cabbage, broad beans, carrots, and turnips, potatoes, and ordinary butcher's meat. We are of the opinion that cheese, rich cakes, rich sauces, pastry, and condiments are definitely contraindicated ; and so are all forms of alcohol, especially in the shape of fermented liquors, as beer and stout. The meals should be light and over-eating must be avoided. The evening meal, or dinner, should be the lightest meal of the day, and must be taken of before 7.30 p.m. Any tendency to constipation must be checked by adding more fruit to the dietary or by taking petrolagar. Plenty of fish, chicken, and fruit should be partaken of, and all fatty and starchy puddings should be avoided. Such vegetables as boiled onions and tomatoes appear to be well tolerated after sprue ; but potatoes and starchy foods, such as white bread and haricot beans, do not. After three months of convalescent treatment lean bacon and lean ham may be allowed as an accessory to the dietary.

We consider climate a most important factor. Sprue patients from the tropics do not stand the climate of an English winter well. We have often remarked that sprue relapses appear to be induced either by excessive heat or by excessive cold, so that chronic sprue patients are especially liable to relapse in the long winter months of a northern climate. It is not dry cold weather that seems to affect them so much as cold winds, wet, and dampness of an English winter. Sprue patients have to avoid getting cold and especially chilled by rain and cold winds. Whenever possible, the patient should be advised to spend the winter in an equitable warm climate, such as that of the Canary Islands or Madeira, where a continuous supply of fresh fruit can be obtained. If convalescent sprue patients have to remain in England they should winter in some mild winter resort, such as Torquay, Paignton, or other parts of Devonshire. Sprue patients of Scottish origin should be discouraged from returning to Scotland during the cold weather and spring months. On the other hand, Egypt and North Africa are unsuitable for sprue patients on account of the extremes of temperature during the daytime and also on account of the irritating dust and sand.

For those whose physical condition permit it, walking is by far the best exercise for convalescent sprue cases. This exercise should be graduated and pressed up to the point of slight fatigue. Over-fatigue must be sedulously avoided as being liable to bring on a relapse. Mild golf appears also to be suitable. On the other hand, riding and bicycling must be avoided. Should the patient's employment involve strenuous physical exertions, it is advisable that he should gradually train his body to undertake it for at least six months before he is able to resume full duties.

Conclusions.

It is realized that the conclusions which we have arrived at as the result of this protracted study of our clinical material are somewhat theoretical in nature, but we consider that we have at our command a legitimate substratum of facts for doing so, and we state them merely as forming a basis for future work:

1. That sprue has a wide geographical distribution throughout the tropics and subtropics between the latitudes of 40° N. and 20° S. of the Equator; that, in fact, it has a more northerly than southerly range.

2. That wherever it occurs it is a disease specially liable to affect Europeans and that it is prevalent in them the nearer the Equator is approached; but that in its distribution it tends to miss the whole of the Central African Continent.

3. That wherever it occurs in widely separated localities the nature and symptoms of the disease are identical. Sprue is therefore a disease *sui generis*.

4. That the European victims of sprue are those who for the most part are living in close contact with natives of the endemic area of the disease.

5. That in certain countries where it is prevalent it occurs with greater frequency in certain definitely restricted zones, such as the cities of Bombay and Colombo and the Treaty Ports of China.

6. Although sprue in native races is rare, yet it can be recognized in Indians by its unmistakable signs, and it is possible that it exists in other races to an extent not recognized in a larval and less easily detectable form.

To our minds these facts point to the probability of sprue being an infective condition contracted from the native population which, as in the case of other well-known tropical diseases, may harbour the infection.

These conclusions are supported by the following considerations:

(*a*) Sprue has a definite incubation period.

(*b*) It is subject to definite periods of latency and recrudescence.

(*c*) There is evidence of a specific inflammation ranging through the whole intestinal tract and affecting principally the processes of digestion and assimilation. The nature of the virus may be ultramicroscopic and of a low grade specificity which can only be acquired in the tropics under certain definite conditions and from long contact with native races.

(*d*) We must assume that the virus is capable of lying dormant in a larval form in the human body for a number of years, and in this manner we may explain the manifestations of sprue symptoms many years after quitting an endemic zone of the disease.

(*e*) There is evidence that recovery from the disease depends to a great extent upon restoring the functions of absorption.

(*f*) That the anaemia of sprue is dependent in the first instance on the destruction of the intestinal mucosa and the lack of nutrition of the tissues thereby entailed, while the cure of the anaemia is followed by amelioration of the intestinal symptoms and generally by an increase in the power of absorp-

tion, probably by augmenting the general blood supply and nutrition of the bowel wall.

(g) There is evidence that cases of sprue of the more severe type with high grade anaemia and bowel symptoms are completely restored to health whenever the blood picture is restored to normal as by blood transfusion. This in turn leads to an apparent cure of the bowel symptoms in cases which have now been observed over a number of years.

(h) The cure of sprue depends upon the administration of a nutritious and easily-assimilable dietary with the addition of protein and liver in order to stimulate the haemopoïetic functions of the bone marrow.

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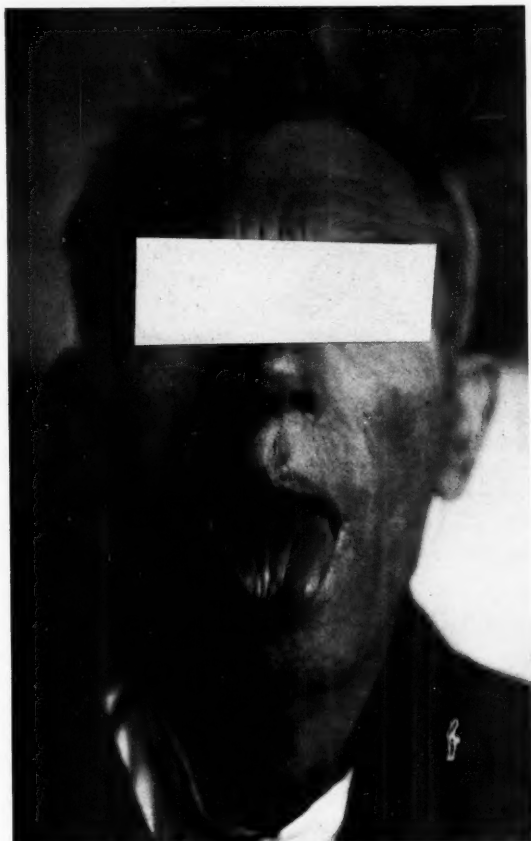
FIG. 1. The polished appearance of the atrophic sprue
tongue and the general facies of sprue

FIG. 2. Illustrates the extreme meteorism of the lower abdomen in chronic sprue

FIG. 3. Patchy brown pigmentation as seen on the face
of the anaemia of sprue

FIG. 5. Type of extreme emacia-
tion in sprue showing distension
of abdomen

FIG. 6. A case of extreme emaciation in sprue of seven months' duration.
Indian infection. Weight 106 lb. Normal weight 168 lb.

FIG. 7. Appearance of patient on 24/10/1925, before commencement of treatment. Weight 88 lb.

FIG. 8. Photograph of the same case (No. 98) on 5/1/1926, after a course of dietetic treatment. Weight 158 lb.

THE MEASUREMENT OF SKIN TEMPERATURES [1]

By F. CAMPBELL SMITH and S. LEVY SIMPSON

In the course of some investigations on peripheral circulation, it was found necessary to employ a rapid and reliable method of measuring surface temperature. In order to secure this, and also to satisfy a further requirement of portability, one of us (F.C.S.) devised an apparatus which appears to have several advantages over the conventional thermocouple with its control thermostat (1). Essential details of this apparatus, with a description of its clinical application, are given below.

Description of Instrument for Measuring Surface Temperature.

It has long been recognized that no form of mercurial thermometer is suitable for the measurement of skin temperatures. The alternative has been the use of the thermo-electric method. This method has recently been employed, with considerable success, by Lewis and Wolf (2), Benedict (3), and others.

Although the method is quite satisfactory for making such a physical measurement, its disadvantages in clinical practice are many. A very sensitive and not easily portable galvanometer must be employed to measure the current produced by the thermocouple chosen. The couple which is not applied to the skin must be kept at a constant temperature by some thermostatic device (Benedict, 1927). The junction itself is easily broken, and requires special protection and careful handling. It is manifestly a method which can only be used by persons with special training and having a considerable knowledge of the principles of physical measurement. It was the present writers' object to devise a method which would measure skin temperatures with sufficient accuracy for clinical purposes and which could be safely left in the hands of an unskilled operator.

The platinum resistance thermometer affords an alternative method for the measurement of temperature. To the best of the writers' knowledge, this has not been successfully applied to the measurement of skin temperatures. Before describing the experimental technique in detail, its special advantages will be discussed.

1. *The galvanometer.* A microammeter of the uni-pivot type is sufficiently sensitive. When locked, this instrument is safely portable, and measures about

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[1] Received April 4, 1930.

7 by 7 in. by 2 in. in depth. The scale of the instrument can be calibrated in degrees, and therefore gives a direct reading.

2. *The thermometer.* This can be constructed, as will be described later, so that it is strong and requires only ordinary care in handling. Since the thermometer forms one arm of a Wheatstone bridge, a thermostat, which is essential in the case of the thermoelectric method, is not required.

3. *Portability.* The whole apparatus can be constructed so that it is self-contained in a case measuring not more than 9 by 9 in. by 6 in. in depth, weighing only two or three pounds.

Experimental.

The principles of platinum thermometry are well known and so do not need description here. Fig. 1 shows the values of the resistances used by the writers. Over the range of temperature required for clinical work the change of resistance of the platinum with temperature can be taken as linear: the galvanometer will therefore give a direct reading. In this connexion it is very important that the potential difference across the bridge should be the same for all observations. In order to check this, the switch S_2 (Fig. 1) is turned so that the test resistance R_2 now takes the place of the thermometer in the circuit. This resistance is that of thermometer at 30° C. The galvanometer needle is brought to this reading by adjustment of the variable theostat R_1 and the switch S_2 returned to its original position.

The thermometer[1] consists of a platinum wire (No. 48 gauge) wound in a flat spiral and cemented to the end of an ebonite rod. The wire is insulated by a very thin coating of insulating material, and is held in place by a thin film of celluloid varnish. The diameter of the disk applied to the skin is about 8 mm. The resistance of the thermometer is 50ᵂ, and the temperature can be read to 0·05° C., with a galvanometer as described above.

The Application of the Thermometer.

In order that a reading may be obtained in a minimal time (3–6 seconds), it is necessary to bring the thermometer to a temperature as close as possible to the skin temperature which is to be measured. This is done by holding the surface of the instrument on the palm of the operator's hand for half a minute. The current to the bridge is then switched on. When the galvanometer needle has become steady, the thermometer may be applied to the portion of skin required. A reading should be obtained within the time prescribed above. The same precautions were found necessary by Benedict (3) and Lewis and Woolf (2) when using the thermo-electric method, and are fully described in their papers.

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[1] The thermometer and other component parts of the apparatus in a portable form may be obtained from Messrs. Griffin and Tatlock, Kingsway, London.

Clinical Application and Method of Use.

The measurement of surface temperature has a wide field of clinical application. It is an essential factor in investigating disorders of the peripheral blood vessels, such as Raynaud's disease and thrombo-angeitis obliterans, and the effects of sympathetic ganglionectomy. The French investigators have advocated the Pachon oscillometer as a suitable instrument for studying circulatory disorders. Although the oscillometer is helpful in diagnosis, its further uses are limited. Calorimetric methods are admittedly of great value, but, compared with surface temperature measurements, are more cumbersome and time-absorbing.
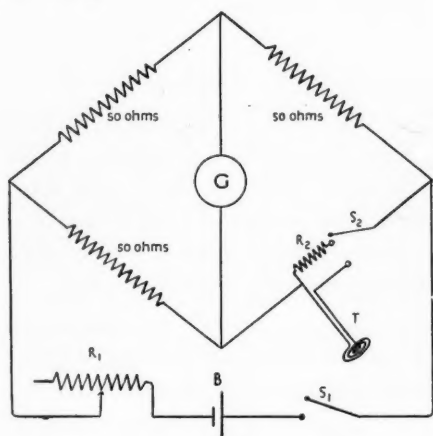

FIG. 1.

R_1 = Variable resistance, about 10 ohms.
R_2 = Equivalent resistance of thermometer at 30° C.
S_1 = Switch, for battery.
S_2 = Two-way switch.
T = Resistance thermometer.
G = Galvanometer.
B = Battery.
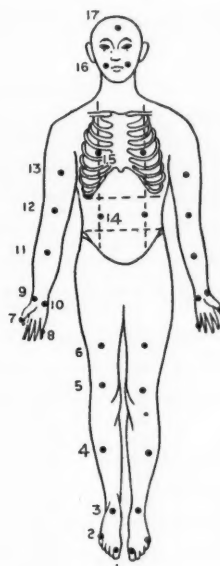
FIG. 2.

Although the use of the instrument described above is both easy and rapid, there are several precautions to be observed.

1. *Conditions of exposure and temperature measurement.* The surface temperature depends not only on the circulation beneath the skin but also on radiation, convection, conduction, and vaporization. The marked effect of exposure can easily be seen by taking the temperature at intervals of a few minutes following exposure. In comparing temperatures of two limbs following, for example, unilateral ganglionectomy, (*a*) corresponding points must be measured within a few seconds of one another, (*b*) the conditions both before and during the exposure must be the same.

2. *Point of application.* Parts of the skin near large blood-vessels (e. g. under the knee) are naturally warmer than those more remote (e. g. knee

cap), but it is perhaps difficult to realize that two points separated by as little as 1·5 cm. may have an appreciable difference of temperature. It is therefore essential to demarcate clearly with tape measure and blue pencil the exact point of application of the thermometer.

3. *Mode and time of application.* The surface of the thermometer is applied lightly to the point indicated. When dealing with small surfaces, e.g. fingers and toes, it should be seen that the whole area of surface is in contact with skin. A constant reading of the thermometer should be obtained within a few seconds. This, however, is only true if the temperature of the platinum coil is near to that of the skin before its application. The thermometer should be left at its last point of contact until everything is ready for rapid transference to the next point.

Observations Illustrating Use of the Thermometer.

A diagram is appended which suggests some points of application, and the results are tabulated in the Table. The numbers used for corresponding points on both sides of the body are the same, the word 'right' or 'left' being noted after them. It is convenient for the investigator to have a chart by him, and for the recorder to mark the readings on a corresponding chart or table. With practice the recorder can both read the galvanometer and make the record.

	Normal.		Normal (after cooling with ether).		Raynaud's Disease.		Intermittent Claudication.	
	R.	L.	R.	L.	R.	L.	R.	L.
1	21·4	21·2	—	—	15·8	14·3	19·5	20·0
2	22·4	22·0	—	—	15·0	14·3	20·1	20·0
3	27·0	27·0	—	—	20·0	19·5	24·8	24·6
4	32·5	32·3	—	—	22·5	21·5	28·8	28·9
5	31·0	31·0	—	—	23·6	23·6	28·7	28·6
6	32·3	32·6	—	—	27·0	26·8	—	—
7	26·6	26·8	23·6	—	17·6	16·8	27·5	27·3
8	26·0	26·0	22·0	—	15·8	15 8	26·0	25·8
9	28·0	27·9	24·22	—	20·4	20·0	30·0	29·6
10	27·4	27·8	24·0	—	20·4	20·1	28·4	28·5
11	31·0	30·8	26·0	—	27·8	28·0	31·5	31·5
12	32·6	32·6	28·6	—	—	—	32·6	32·9
13	33·0	32·8	—	—	—	—	—	—
14	35·1	35·2	—	—	—	—	—	—
15	33·9	34·0	—	—	—	—	—	—
16	35·0	35·1	—	—	—	—	—	—
17	33·9	33·9	—	—	—	—	—	—

Measurements in °C. Room temperature 16·2° C.

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THE ACTION OF HISTAMINE ON THE CHLORIDE CONTENT OF THE STOMACH [1]

By R. J. DUTHIE

(From the Aberdeen Royal Infirmary)

WITHIN the last few years knowledge of the physiology of the stomach has been increased considerably by investigations regarding the regulation of gastric acidity. Maclean and his colleagues (1), (2), (3), (4) have put forward evidence of the secretion of the chlorine ion partly as hydrochloric acid, and partly as sodium chloride, and have demonstrated that the fall in the concentration of acid at the end of digestion is due not to regurgitation of alkaline fluid from the duodenum, as formerly supposed, but to increased secretion of neutral chloride. In view of this regulation of gastric acidity by the varying secretion of neutral chloride, in the following investigation observations have been made regarding the relationship between the concentration of hydrochloric acid and total chloride before and after the injection of histamine, which is now a well-known stimulant of gastric acidity.

The stomach contents of fourteen patients were examined both before and after the subcutaneous injection of 0·25 mg. of histamine. This dose was decided upon because it has been shown by Gompertz and Cohen (5) to be a satisfactory stimulant of gastric hydrochloric acid, and insufficient to cause any serious disturbance which often accompanies larger doses. In each case, after a sample of the resting contents had been removed by means of an ordinary small bore stomach-tube, 50 c.c. of 7 per cent. alcohol were injected through the tube into the stomach. Cheney (6) has suggested that this amount of alcohol is a suitable gastric stimulant. This eliminates many technical difficulties, such as great dilution of the gastric acidity, the buffer action, and the psychic stimulus accompanying a cereal test meal. The acidity (determined by using methyl orange as an indicator) and the total chloride concentration were estimated immediately before, and half an hour after, the alcohol injection. The alcohol test was repeated on each patient one or two days later with the addition of a subcutaneous injection of 0·25 mg. of histamine immediately after the alcohol. Though there was invariably a drop in blood-pressure of about 10 mm. Hg., in no case were there any untoward symptoms after the injection of histamine.

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The results obtained confirm the above-mentioned authors' findings that the dose of 0·25 mg. of histamine is a safe and efficient gastric stimulant.

It may be mentioned that, on the second examination, the resting gastric contents were not always found to have the same free acidity and total chloride concentration as on the first. In the present investigation, however, the condition of the stomach half an hour after the injection has only been considered. The cases consisted of patients suffering from various gastric conditions, including two examples of achylia gastrica.

The results obtained are as follows :—

Table showing concentrations of free hydrochloric acid and total chloride, both before and after histamine injections.

| | Grm. per 100 c.c. | | | | Increase after histamine. Terms of NaCl %. | |
| | After alcohol. | | After alcohol and histamine. | | *A.* | *B.* |
	HCl.	Total Cl.	HCl.	Total Cl.	HCl.	Total Cl.
1	0·108	0·564	0·259	0·580	0·243	0·016
2	0·184	0·551	0·458	0·666	0·458	0·115
3	0·132	0·551	0·360	0·607	0·367	0·056
4	0·108	0·385	0·211	0·546	0·166	0·161
5	0·108	0·374	0·144	0·436	0·058	0·062
6	—	0·258	—	0·378	—	0·120
7	—	0·202	—	0·436	—	0·234
8	0·072	0·373	0·096	0·407	0·039	0·034
9	0·126	0·492	0·330	0·695	0·329	0·203
10	—	0·202	0·126	0·373	0·203	0·171
11	0·288	0·607	0·324	0·895	0·058	0·288
12	0·262	0·546	0·413	0·695	0·243	0·149
13	0·096	0·461	0·078	0·522	−0·029	0·061
14	0·054	0·364	0·054	0·461	—	0·097

In the above results, column *A* represents the increase in concentration of chloride due to the increased secretion of hydrochloric acid after the subcutaneous injection of histamine. Column *B* represents the increase in the total chloride concentration, that is, including the chloride of the hydrochloric acid. It will be observed that, in the fourteen cases examined, there is an increase in total chloride concentration in all cases (column *B*). In eight cases, namely, numbers 1, 2, 3, 4, 8, 9, 10, and 12, the increase in total chloride is less than the increase in chloride that can be accounted for by the increased acidity.

None of the cases in the present investigation showed evidence of duodenal regurgitation by the presence of bile, and the results would seem to bear further evidence that the regulation of acidity occurs in the stomach. There is a rise in total chloride concentration in all cases without duodenal regurgitation. Further, it would appear that, in the eight cases above mentioned, injections of histamine cause a change in the proportion of hydrochloric acid and neutral chloride secreted in the stomach by stimulating the secretion of the chlorine ion as hydrochloric acid, and diminishing the secretion of the ion as neutral chloride.

In other words, the increase in hydrochloric acid after histamine injections takes place at the expense of neutral chloride.

For various helpful criticisms I wish to thank Dr. W. F. Croll, in whose wards the investigation was made, and Professors J. J. R. Macleod and C. R. Marshall.

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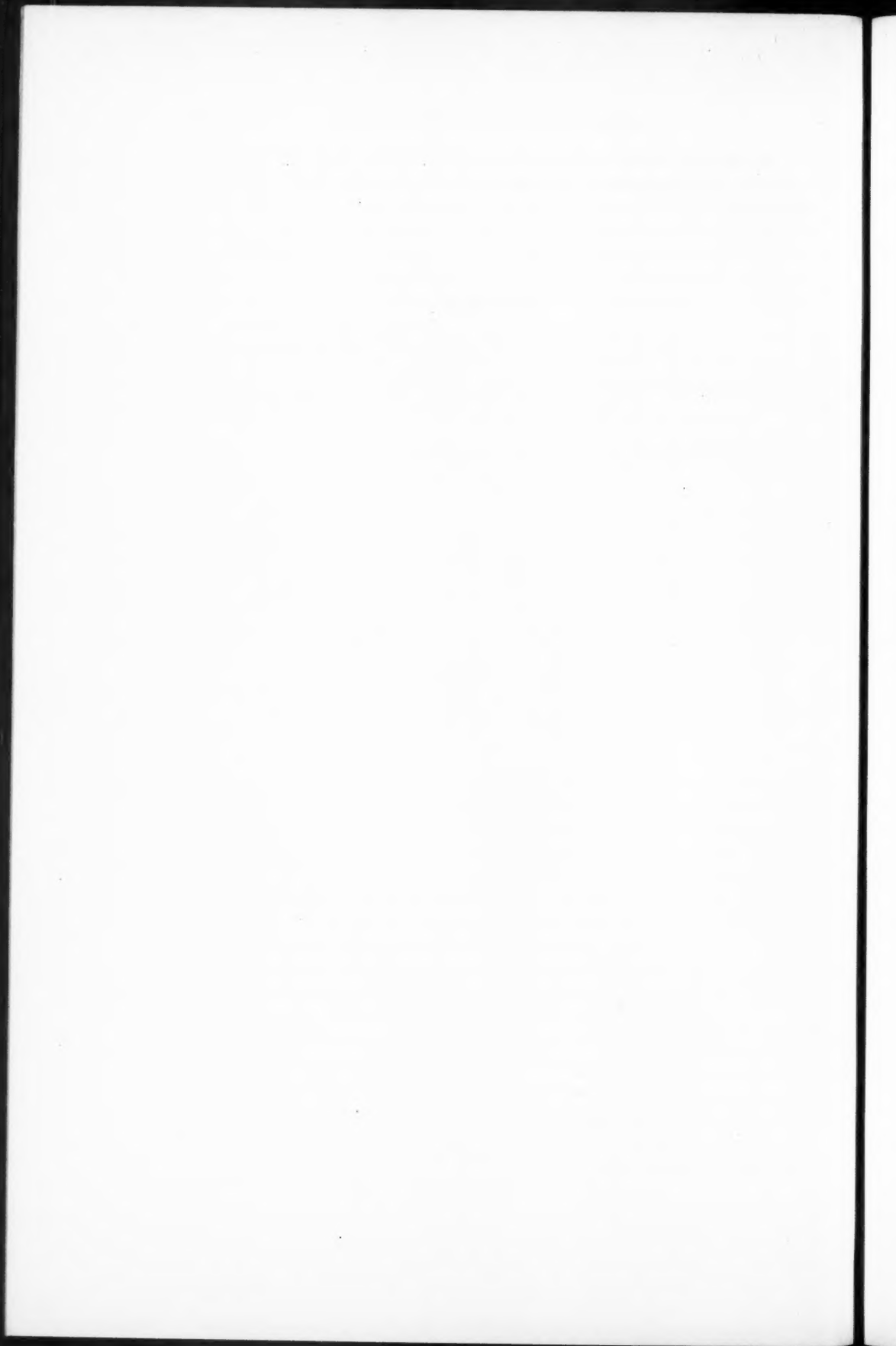
THE VISCOSITY OF THE BLOOD IN HIGH BLOOD-PRESSURE [1]

By I. HARRIS and G. McLOUGHLIN

(From the Liverpool Heart Hospital)

Introduction.

IN this paper an attempt is made to discover whether a relationship exists between high blood-pressure and the viscosity of the blood.

The blood-pressure depends on cardiac output and the resistance to outflow at the peripheral end of the circulation. This resistance is due to contraction of the small vessels and the thickness or viscosity of the blood. It is conceivable that an increase in viscosity of the circulating fluid may give rise to a compensatory high pressure. Such consideration on purely theoretical grounds led Clifford Albutt (1) and others to believe that viscosity plays an important part in cardiovascular disease. As soon, however, as an attempt was made to solve the problem by experimental methods it was found that no relationship could be shown to exist between the rise of pressure and the rise in viscosity in the healthy individual. Large doses of gelatin were injected into the circulation, and as a result the blood viscosity was found to be considerably increased, yet the blood-pressure remained normal (2). In this instance, as well as in many others, the regulative activity of the organism which keeps the pressure in a certain equilibrium came into play. Either dilatation of the peripheral vessels or alteration in cardiac output may counteract the effect of increased viscosity on the circulation. The question, however, remains as to whether in diseases such as arterio-sclerosis, where compensatory dilatation is likely to be more difficult, a high viscosity of the blood might not give rise to a high blood-pressure.

Some authors, like Bachman and Wells (3), maintain that no relationship exists between these two conditions. On the other hand, Determan (4) and others found that there is some relationship between viscosity and blood-pressure when the latter is abnormally high or abnormally low. Martinet (5) divided his cases into three groups. In the first group he included those which show an increase in blood-pressure and a corresponding rise in viscosity. In the second group those with a low viscosity and a high pressure. In the third group those which show high viscosity and a low pressure. It follows that, according to this author, a high pressure may be found in conjunction with

[1] Received March 27, 1930.

a high or low viscosity ; in other words, there is no relationship between these two conditions. Lyon's (6) work on viscosity in relation to high pressure is inconclusive.

Plan of the Investigation.

1. To determine the blood viscosity in cases of normal blood-pressures. For the purposes of this work pressures between 110 mm. and 160 mm. were considered to be normal.
2. To determine the viscosity (*a*) in cases of high pressure ; (*b*) in cases of low pressure.
3. To correlate over lengthy periods daily variations in pressure and viscosity readings in cases of abnormally high blood-pressure.
4. To determine the effect on the blood-pressure of artificially lowering the viscosity.
5. To determine the effect on viscosity of artificially lowering the blood-pressure.
6. To determine the effect, if any, of starvation on the relationship between the blood-pressure and blood viscosity.
7. An attempt was made to discover the factors responsible for the increase of viscosity.

Method.

The various viscosimeters in use are based on different principles, and it is therefore not surprising that the different methods do not quite yield the same results. It would be helpful if some standard viscosimeter were to receive general recognition. As it is, it is essential to use the same instrument in all viscosity determinations. The apparatus used for the purpose of this investigation was the Hess viscosimeter ; it is so well known that a description of it is not necessary.

The principle underlying this instrument is based on Poiseuille's Law, which states that fluids under equal temperature and pressure passing through capillary tubes of equal radius vary in their rate of flow in direct proportion to their viscosities. All the estimations were carried out at a constant temperature of 15° C.

A drop of blood taken from the capillaries was used, just sufficient for a capillary tube three inches long, having a bore about one-third of a millimetre. At the commencement hiridin was used to prevent coagulation. It was, however, found that hiridin is unnecessary. Oxalic acid was found to interfere with the results and therefore was not used.

A determination of the serum viscosity was not undertaken. In any event serum viscosity forms only about one-third of the total blood viscosity.

The blood-pressure was taken by means of the Riva Rocci apparatus. Other methods of investigation will be mentioned in the text.

I. *Viscosity Readings in Normal Cases.*

The following Table gives the results of a number of examinations of 21 more or less normal cases who attended the hospital out-patient department for some trivial conditions.

TABLE I.

Sex.	Systolic Pressure.	Viscosity (Water = 1·0).	Sex.	Systolic Pressure.	Viscosity (Water = 1·0).
M.	120	5·9	F.	120	6·0
M.	120	5·8	F.	145	5·4
M.	120	5·3	F.	125	5·0
M.	120	5·9	F.	120	5·3
M.	120	5·4	F.	115	4·9
M.	130	5·4	F.	120	4·8
M.	120	5·3	F.	120	5·0
M.	120	5·0	F.	125	5·1
M.	120	5·2	F.	115	5·0
M.	130	5·3	F.	112	5·9
F.	130	6·3			

Of these cases, ten were males, and eleven females. The average viscosity for the former was 5·45, with a range of 5 to 5·9, while the latter showed an average viscosity of 5·3, with a range of 4·8 to 6·1.

It is interesting to note here that Hess, in his investigations, found that adult males showed an average viscosity of 4·7, with a range of 4 to 5·5, while the average for females was 4·4, with a range of 4 to 5·4. He considered that viscosity values of below 4·3 and above 5·3 in males, and below 3·9 and above 4·9 in females, were abnormal.

According to Hirsch and Beck (7) the normal range of viscosity reading is 4·50 to 5·89. According to Bence (8), 4·37 to 6·80. According to Determan (9), 4·05 to 5·54.

Daily variations in range of viscosity is common according to Blunschy (10). This variation comes to about 12 per cent. of total viscosity readings, though in a few extreme cases they may vary as much as 30 to 40 per cent. of the total reading.

Taking 5·45 and 5·3 as the average viscosities for males and females respectively, as found in this investigation, we can reasonably consider any viscosity above 6 or below 4, whether for male or female, to be abnormal.

II A. *Cases of Abnormally High Pressure.*

These consisted of unselected cases of abnormally high pressure. Out of forty cases there are only five which give a viscosity reading which is within normal limits. The average viscosity of these forty cases of abnormally high blood-pressure is 7·715, or 2·265 units higher than the mean viscosity of the normal cases.

It is clear from this Table that there must be some relationship between

high pressure and high viscosity, otherwise the high viscosity readings obtained would be difficult to explain.

It will also be seen that it is possible to have a case of high blood-pressure with a normal viscosity reading.

It must not be assumed, however, that in every case of high viscosity there will be found a corresponding increase in pressure. This is illustrated by a case of congenital heart disease, which was admitted to the Liverpool Heart Hospital. The patient, a female, showed a viscosity of 19·6, associated with a blood-pressure of only 120 mm. The red blood cell content was 8,650,000.

TABLE II. *Cases of Abnormally High Blood-pressure.*

Sex.	Systolic Blood-pressure.	Viscosity.	Sex.	Systolic Blood-pressure.	Viscosity.
F.	270	11·0	M.	190	7·6
F.	148	10·4	M.	220	7·4
F.	265	10·0	M.	184	7·4
F.	250	9·6	F.	190	7·3
M.	200	9·4	F.	190	7·2
F.	235	9·2	M.	190	7·2
M.	240	9·2	F.	215	7·2
F.	210	8·8	F.	176	7·0
M.	210	8·6	F.	260	7·0
F.	245	8·4	F.	170	7·0
F.	190	8·4	F.	160	7·0
F.	245	8·4	F.	252	6·8
F.	246	8·4	F.	204	6·7
F.	200	8·4	F.	230	6·4
F.	230	8·3	F.	240	6·1
F.	260	8·0	F.	166	6·0
M.	216	8·0	M.	190	5·9
M.	224	7·6	F.	156	5·7
M.	170	7·6	M.	170	5·2
F.	180	7·6	F.	230	5·2

II B. *Cases of Abnormally Low Blood-pressure.*

In this group it was only possible to obtain five cases, and out of these only two showed an abnormal lowering of the blood viscosity. The remaining three cases showed a blood viscosity which was within normal limits. So far as it is permissible to derive conclusions at all from such a small number of cases hypotony seems to show a tendency to low viscosity.

TABLE III.

Sex.	Systolic Blood-pressure.	Viscosity.
M.	108	3·7
M.	110	5·9
F.	110	4·9
M.	94	5·6
F.	110	3·9

III. *Normal Daily Variations in Blood-pressure and Blood Viscosity.*

Of the cases of abnormally high blood-pressure, seven—all females—were examined to determine whether there existed any relationship between the daily fluctuations of blood-pressure and blood viscosity.

The cases were admitted to Hospital and kept on an ordinary diet for a period of seven to eight days. The blood-pressure and blood viscosity were estimated daily during this period, care being taken that the readings were determined at the same time each day. No treatment whatever was given.
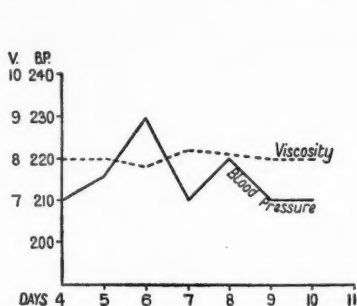
GRAPH I.
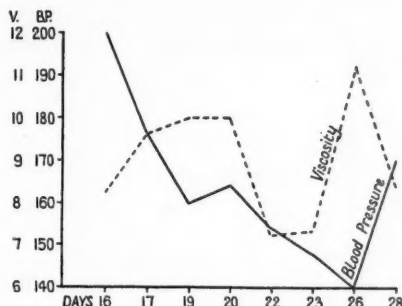
GRAPH II.

The results obtained are shown in the accompanying graphs. Two typical cases are illustrated in the Graphs I and II on this page, whilst the other results are shown in the Graphs V and VI in the Appendix. It must be borne in mind, however, that the methods of recording blood-pressure and viscosity are not sufficiently accurate to depend on them for measuring slight variations. In addition, blood-pressure and viscosity are influenced by many factors which come into play.

IV. *To Determine the Effect upon Blood-pressure of Artificially Lowering the Viscosity.*

It was accidentally discovered by one of us (I. H.) that the imbibing of large quantities of fluid frequently had a striking effect in lowering blood-pressure, which in many instances remained low long after the intake of fluid had been discontinued. It was in order to discover an explanation for this action that this investigation was undertaken in the first instance.

In each case the patient was kept on a standardized diet throughout the treatment. For the first seven days no drugs were given and an ordinary amount of fluids allowed. From the eighth to the fifteenth day the fluid intake was increased to six pints daily—mostly in the form of water. On the fifteenth day the extra fluid was discontinued and the ordinary daily quantity given for a further seven days.

The results are shown in the accompanying graphs. Graph III on page 456 and Graphs VII, VIII, and IX in the Appendix explain themselves. From viscosity and pressure readings shown in these graphs it appears extremely likely that the fall in blood-pressure following the intake of large quantities of fluid is due to a reduction of viscosity.

The parallelism between a lowering of viscosity, fall of pressure, and increased urinary output is very striking in some cases, less striking in others. A uniform effect cannot possibly be expected to result from variations of pressure and viscosity, seeing that each depends on factors so many and so variable. In fact there is no method of treatment of these
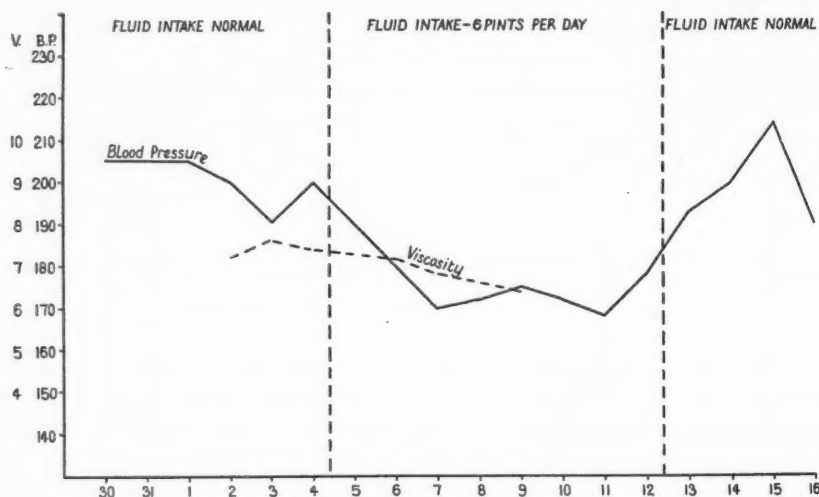
GRAPH III.

conditions which yields uniform results in all cases. The important fact is that there are cases of high blood-pressure—the majority of cases under our observation—in which a high viscosity is a sole or contributory cause of high pressure and which yields to treatment by the simple means of intake of large quantities of fluid.

V. *To Determine the Effect of the Viscosity of Artificially Lowering the Blood-pressure.*

Attempts were made to bring about a fall in blood-pressure by the use of drugs. Two drugs were employed—collosol sulphur and erythrol tetranitrate. As would be expected the collosol sulphur showed the more dramatic results.

Three cases were treated with collosol sulphur, but of these only two yielded results within the province of this investigation. The third became extremely ill after the first administration, and the treatment had to be discontinued.

The patients were kept for a period of six to seven days without treatment. An initial dose of 2 c.c. of collosol sulphur was given intramuscularly on about the seventh day, and repeated in four and eight days. The blood-pressure and blood viscosity were estimated daily.

The results obtained were very striking, so far as they brought about a fall in blood-pressure, but they showed no effect on the blood viscosity.
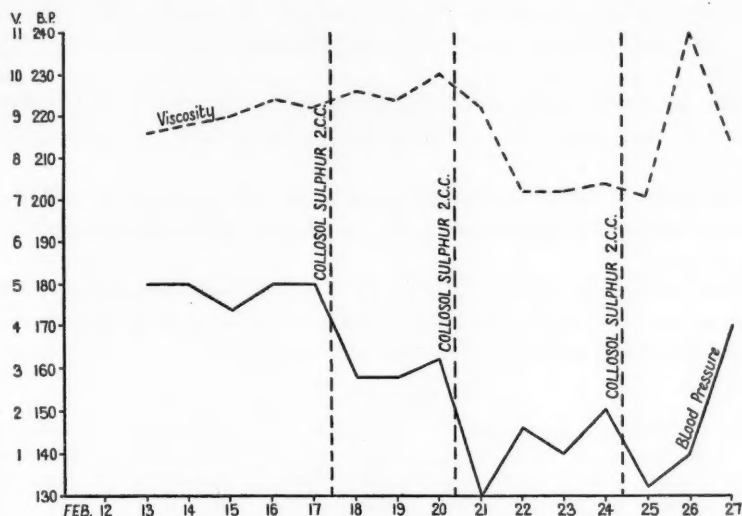
GRAPH IV.   Mrs. J.   To show the effect of collosol sulphur on blood-pressure and viscosity.

The first patient's record shows that on the day of and prior to the first injection she had a blood-pressure of 260 mm. Within twenty-four hours after this injection the pressure had dropped to 190 mm., but the blood viscosity remained more or less constant. After the second injection the blood-pressure reached a minimum in forty-eight hours, falling to 170 mm., while the blood viscosity recorded was actually 0·4 units higher than that existing with the initial blood-pressure of 260 mm.

Following the third injection the blood-pressure fell to 150 mm., but there was no further alteration in the blood viscosity.

The graph of Case 2 (IV) shows very similar results. The blood-pressure fell after the first administration, and the blood viscosity remained more or less constant. After the second injection there was a fall of both blood-pressure and blood viscosity. But after the final injection there was a very marked rise in viscosity—from 7·1 to 11—associated with a rise in blood-pressure of only 8 mm.

With regard to these results, it must be remembered that collosol sulphur acts solely on the peripheral vessels, so that it is not surprising that the fall in blood-pressure was not associated with a corresponding fall in blood viscosity.

Two cases were treated with erythrol tetranitrate, but as they did not show any striking results it would be useless to consider them here. A graph is, however, shown in the Appendix—(X).

VI. *To Determine the Effect of Starvation on Blood Viscosity.*

The routine carried out in these cases was as follows : On the day previous to the investigation the patient was given supper at 7 p.m. From that hour until noon the following day no food was allowed, except half a pint of tea at 7 a.m.

The viscosity of the blood and the blood-pressure were estimated at 10.30 a.m. and at 12 noon, when the patient would be starving for $15\frac{1}{2}$ and 17 hours respectively.

An ordinary dinner was given at 12 noon, and the viscosity and blood-pressure were again estimated at 1.30 p.m., 3 p.m., and 4.30 p.m.—tea being given at 4 p.m.

From the results shown in Table IV it will be seen that the viscosity is definitely increased during starvation, but that there is no definite relationship between changes in blood viscosity and blood-pressure.

TABLE IV.

	10.30 a.m.		12 p.m.		1.30 p.m.		3 p.m.		4.30 p.m.	
	B.-P.	V.	B.-P.	V.	B.-P.	V.	B.-P.	V.	B.-P.	V.
I	220	9·6	210	9·6	210	8·2	220	8·3	200	8·5
II	190	9·2	220	9·2	216	8·0	210	8·3	200	8·6
III	180	8·9	200	8·9	190	7·6	190	7·8	200	8·1
IV	190	9·1	180	9·1	200	8·2	200	8·4	196	8·5
V	190	10·2	190	10·2	200	6·4	190	8·4	180	8·8
VI	230	6·2	220	6·2	180	5·8	210	5·8	220	6·0
VII	204	10·4	180	10·4	190	7·8	180	8·8	200	9·6
VIII	190	10·2	190	10·2	200	6·9	190	7·4	180	8·4
IX	170	8·7	165	8·7	180	6·8	170	7·1	170	7·5
X	160	6·4	165	6·4	180	5·7	170	5·9	175	6·0
XI	190	9·1	180	9·2	195	7·0	195	7·5	190	7·9
XII	210	7·9	200	7·9	200	6·4	210	6·8	215	7·0
XIII	175	8·3	175	8·3	200	6·8	180	7·1	185	7·3
XIV	160	8·7	160	8·7	165	5·9	160	6·4	150	6·7
XV	180	7·0	180	7·0	185	5·8	185	6·1	180	6·3

VII. *Factors Responsible for the Increase of Viscosity.*

An attempt was made to determine the factors responsible for the increase of viscosity found in cases of high blood-pressure. It is known that increase in the number of red cells or an increase in the size of the cells brings about an increase of viscosity, and with reference to the former the following Table constructed by Bence (11) may be of interest :—

TABLE V.

No. of Red Cells.	Viscosity.
6,710,000	6·48
7,368,000	8·10
8,364,000	17·30
9,344,000	20·90

In a case of congenital heart disease mentioned earlier in this paper, the red cells numbered 8,650,000 and the viscosity was 19·6.

With regard to the other cause for an increased viscosity, the size of the cell is known to vary with the amount of CO_2 present in the blood, and there is usually supposed to be a parallelism between the two. Determann (12) has produced congestion of the arm by stopping the venous circulation, and he found that there is a definite relation between the duration of the stasis point, viscosity point, and CO_2 in the blood. The longer the duration of the stasis the greater the CO_2 content of the blood and the higher the viscosity.

Table VI relates to viscosity, haemoglobin, and cell content.

TABLE VI. *A representative Table of the cases examined, to show the relationship between viscosity, red cell content, and haemoglobin content.*

Systolic Blood-pressure.	Viscosity.	Red Cell Count.	Haemoglobin %.
240	6·1	5,600,000	86
190	6·2	5,600,000	76
170	5·8	5,500,000	86
166	6·0	5,280,000	84
270	8·4	5,200,000	78
200	5·3	5,105,000	78
200	9·4	5,104,000	90
184	10·4	5,100,000	88
215	7·2	5,072,000	88
190	7·3	5,032,000	84
170	7·0	5,010,000	75
170	5·2	4,900,000	70
180	7·6	4,856,000	82
235	9·2	4,850,000	75
180	5·6	4,830,000	80
170	5·2	4,780,000	72
190	7·3	4,700,000	85
230	9·8	4,480,000	79

Tables VII and VIII show the relation of viscosity to the diameter of the corpuscle and volume index. It will be seen that although the diameter and volume index are on the extreme of normal ranges in regard to the size of the corpuscle, the deviation from the normal is not sufficiently pronounced for definite conclusions to be drawn from these figures. The same consideration applies in regard to the number of red cells.

Table IX gives information in regard to the CO_2 content of the blood. It will be seen that the CO_2 content of the blood in the veins is not increased at all; on the contrary it stands on the lower ranges of normal readings.

It can therefore definitely be said that the high viscosity values found in these cases were not due to increased CO_2 content of the blood.

The fact that diuresis and low viscosity run parallel suggests that retention of certain substances by the kidneys might have something to do with high blood viscosity values.

Viscosity is also increased in heart failure. In a large number of these cases the venous pressure was recorded by means of a water manometer for the purpose of another investigation. In the great majority of instances the venous pressure was normal, from which in correlation with other evidence we may conclude that there was no heart failure (13).

Nothing definite, therefore, can be stated in regard to the causes responsible for the high viscosity.

TABLE VII. *Showing the Relationship of Viscosity and Cell Diameter.*

Systolic Blood-pressure.	Average Diameter of Cell in μ.	Blood Viscosity.
190	7·8	8·4
200	7·8	7·0
180	7·65	7·6
190	7·6	8·6
170	7·68	7·6
190	7·36	7·3
200	7·6	8·4
245	7·7	8·4
170	7·6	7·0
252	8·2	6·8
160	8·4	7·0
180	7·7	5·6
190	7·35	7·2

TABLE VIII.

Systolic Blood-pressure.	Average Diameter of Cell in μ.	Volume Index.	Viscosity.
210	7·83	1·09	8·6
180	7·75	1·07	7·6
200	7·78	1·07	9·4
215	7·76	1·06	7·2
220	7·79	1·09	8·0

TABLE IX.

Blood-pressure.	Viscosity.	Venous Blood.		CO_2 tension in pulmonary arteries.
		CO_2 %.	Haemoglobin.	
215	8·4	46·25	92	—
205	7·8	48·0	96	42·321
225	7·6	44·9	86	46·7
170	7·2	40·0	85	41·3
165	6·2	47·58	96	46·81
		Determined by Van Slyck method.		Douglas and Haldane's method.

Discussion.

The evidence is fairly conclusive that the blood viscosity stands in a definite relation to high blood-pressure. The fact in itself that high viscosity is found in the majority of high blood-pressure cases might not necessarily mean that viscosity is a causal factor in these cases. It may simply mean a concomitant condition. But the parallelism of diuresis, low viscosity, and low pressure in cases under large fluid intake is too close and too constant to be explained in any other way but that in some instances high viscosity is a causal factor in high pressure, since by lowering the viscosity we succeed in reducing arterial tension. It is generally recognized that no single factor etiologically is responsible for all the types of blood-pressure : on the contrary, evidence is accumulating

to show that hypertony is caused by a great variety of conditions. Accordingly one cannot expect to find a high viscosity in all cases of hypertony. Very likely too, in cases which give high blood viscosity reading there may be some other and contributory cause for the increased pressure, such as, for instance, abnormal contraction of the small vessels. The fact that in the same cases collosol sulphur and large doses of fluid may lower the pressure suggests that high viscosity and undue contraction of the vessels may be responsible for some types of hypertony. In cases of high pressure when high viscosity is definitely demonstrable the heart is bound to suffer from an increased strain. Obviously such patients would profit by lowering the viscosity through the intake of large quantities of fluid. It is difficult to ascertain the cause of a high viscosity, as has been shown. None of the known factors usually responsible for high viscosity are found in these cases. It may be that the increased diuresis which goes hand in hand with lowering of the viscosity points to hydraemia of the blood and a lower blood count, which might explain the low viscosity. But hydraemia of the blood presupposes an increased quantity of circulating fluid and therefore an increased cardiac action, and a rise in blood-pressure ought to be expected, instead of a fall. No alteration in the blood count was observed as a result of the intake of large quantities of fluid.

It is possible that the intake of large doses of fluid by creating diuresis removes some substances from the circulation which may have caused an increased viscosity.

Conclusions.

1. In the great majority of cases of high blood-pressure the viscosity of the blood is higher than normal.

2. The viscosity of the blood is a causal or contributory factor in high blood-pressure in many instances.

3. The intake of large quantities of fluid lowers the viscosity of the blood and the blood-pressure, the viscosity varying inversely with the urinary output.

4. Intramuscular injection of collosol sulphur lowers the blood-pressure, but has no effect on viscosity.

5. The increase of viscosity in these cases of high blood-pressure is not due to increase in the CO_2 content of the blood, and there is no evidence that it is due to increase in the size or number of the blood-cells.

6. The viscosity of the blood is increased during starvation.

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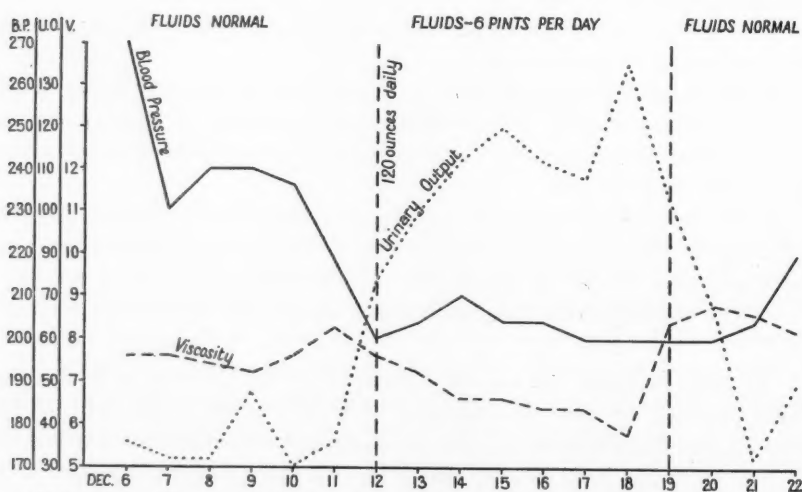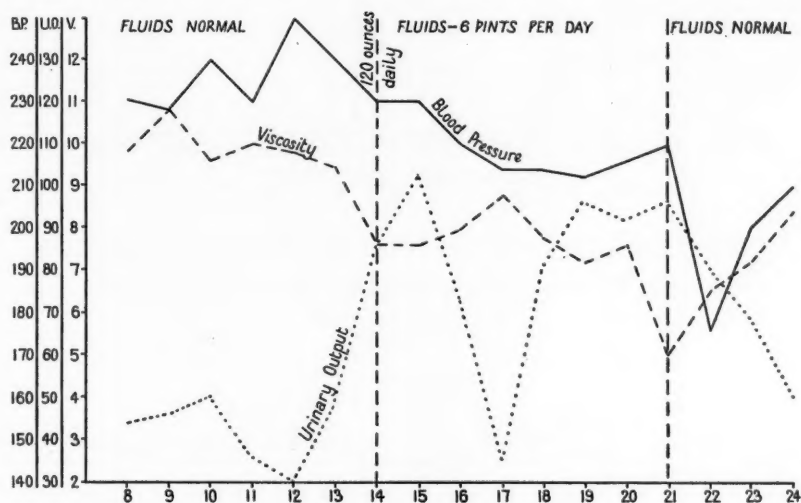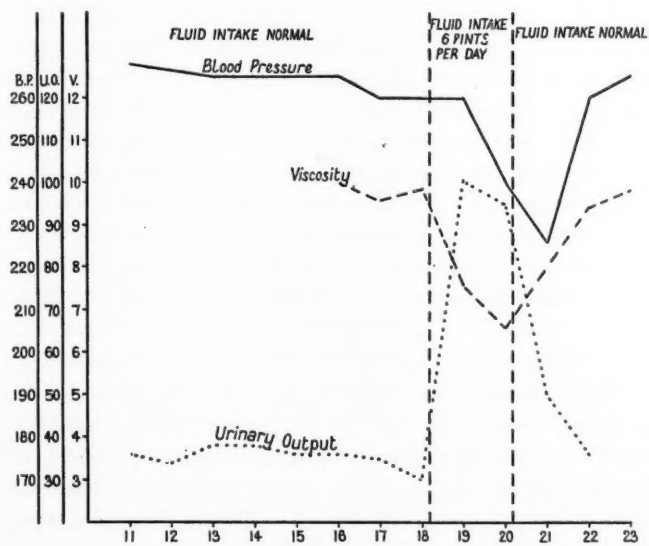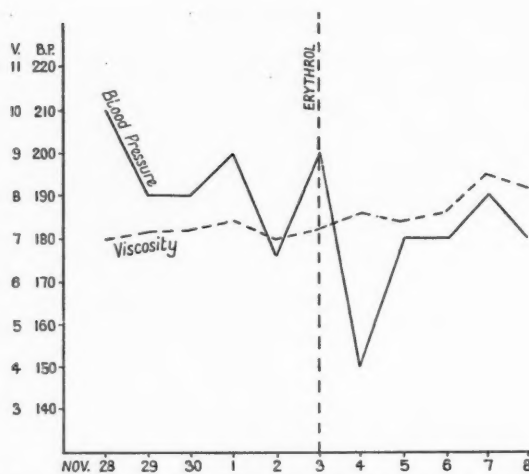
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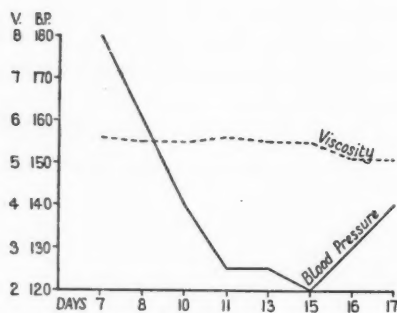
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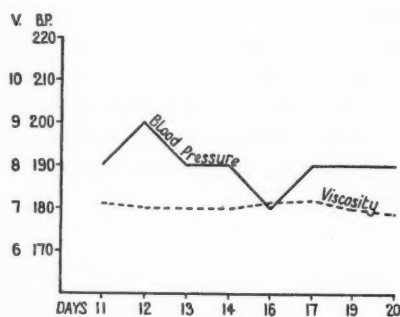
GRAPH VI.

GRAPH VII.   Miss L.   To show the effect of increased fluid intake on blood-pressure and viscosity.

GRAPH VIII. Mrs. M. Showing the effect of increased fluid intake on blood-pressure and viscosity.

GRAPH IX. Mrs. S.

GRAPH X.   Case 2.   Mrs. M.   Effect of erythrol tetra-n. on blood-pressure
and viscosity.

BLOOD CHOLESTEROL STUDIES IN BILIARY AND HEPATIC DISEASE [1]

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General Consideration.

In recent years a large number of papers have appeared in medical litera-
ture dealing with variations from the so-called normal values of the quantities
of cholesterol and its esters found in the blood or the serum of cases of disease of
the liver and of the biliary tract, but in this connexion recent advances on the
chemical side have been largely ignored. In studying the changes in metabolism
in liver and biliary disease, on which we have been engaged for several years,
we have been forced to the conclusion that no adequate explanation can be given
either of our own observations or of those of others without taking careful con-
sideration of the following biochemical facts which have accumulated during
the past fifteen years.

1. Cholesterol is an unsaturated secondary alcohol of the molecular formula
$C_{27}H_{46}O$. It is derived from the parent saturated hydrocarbon, cholestane, $C_{27}H_{46}$,
whose molecule consists of four conjugated hydroaromatic rings and an octyl side
chain (1). Cholesterol occurs in the organism both in the 'free' i.e. alcoholic,
condition and as esters of the higher fatty acids. The most modern view (2)
of its chemical constitution is illustrated in Fig. 1. Various artificial isomers of
cholesterol have been prepared in the laboratory, perhaps the most interesting
being the very labile *allocholesterol*, in which the position of the double linkage
is changed from position 6–7 to position 1–2 (or perhaps 1–13) (6). It is very
readily changed back into ordinary cholesterol.

In *adult* man the waste cholesterol of the body is excreted through the
intestine, for the most part as a mixture of saturated isomeric alcohols $C_{27}H_{48}O$,
viz. β-cholestanol and coprosterol (3, 4, 5), the latter in preponderating quantity.
β-cholestanol is the natural reduction product of cholesterol, produced by satu-
rating the double link with hydrogen. In the formation of the isomeric copro-
sterol, a steric rearrangement of the substituent groups at carbon atom 1 (6) has
occurred in addition, and the parent hydrocarbon is coprostane, a stereoisomer
of cholestane.

[1] Received March 10, 1930.

In this connexion it is significant that the labile allocholesterol is very easily reducible *in vitro* to coprosterol. This would suggest that allocholesterol might occur in the metabolic processes, though our own attempts to detect it have, so far, proved inconclusive.

The formation of coprosterol is generally considered to occur in the gut and to be due to a reduction of cholesterol by the activity of intestinal bacteria, but the evidence for this is, in our opinion, not altogether convincing.

2. The specific bile acids and cholesterol possess the same carbon structure, except that in the bile acids an isopropyl group $(CH_3)_2CH$ has been eliminated from the side chain, and the carbon atom, to which it was attached, oxidized to a COOH group. This relationship will be obvious from a glance at the formulae in Figs. 1 and 2.
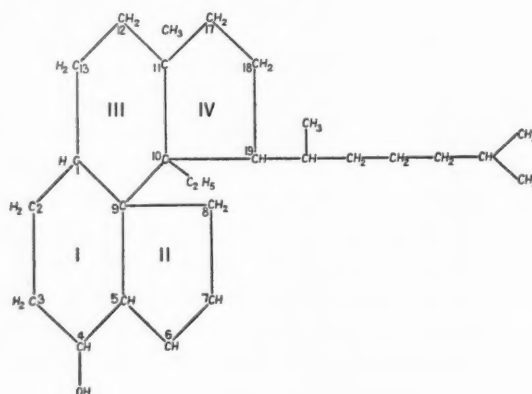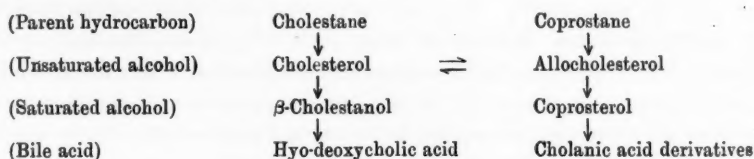

FIG. 1.

It is clear that the sterols and bile acids form a group of substances of analogous structure, which is entirely different from that of the usually-considered metabolic groups, such as proteins, carbohydrates, and fats. Cholesterol and its derivatives are too often lumped together with the fats, lecithides, &c., with which they have not the slightest chemical connexion, under the misleading term ' lipoid '.

The bile acids which have been most studied (7) are those of ox-bile, viz. lithocholic acid (3 oxycholanic acid $C_{24}H_{40}O_3$), deoxycholic acid (3–7 dioxycholanic acid $C_{24}H_{40}O_4$), and cholic acid (3–7–12 trioxycholanic acid $C_{24}H_{40}O_5$), which are hydroxy-derivatives of the parent acid—cholanic acid $C_{24}H_{40}O_2$. In goose, ox, and human bile another deoxycholic acid, with the OH groups in positions 3 and 12, is also found, viz. cheno- or anthropo-deoxycholic acid (18).

These acids, though they do occur as such in bile, are usually coupled with glycine or taurine. They belong to the same stereoisomeric series as coprosterol (7), whose parent hydrocarbon is coprostane (or ψ-cholestane). However, from pig's bile a hyo-deoxycholic acid (3–13 dioxycholanic acid) has been isolated (8), and it is the only naturally-occurring acid, so far found, which

belongs to the same stereochemical series as cholesterol. The following scheme shows these relationships :—

(Parent hydrocarbon)	Cholestane		Coprostane
	↓		↓
(Unsaturated alcohol)	Cholesterol	⇌	Allocholesterol
	↓		↓
(Saturated alcohol)	β-Cholestanol		Coprosterol
	↓		↓
(Bile acid)	Hyo-deoxycholic acid		Cholanic acid derivatives

It is important to note that in vertebrate animals the only sterol isolated from tissue substance is common cholesterol ; whereas many different bile acids have been isolated from different species of animals. Furthermore, in the different animals the acids, even though the same, are present in very different
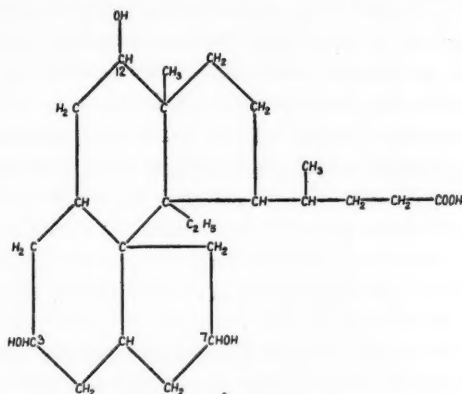

Fig. 2.

relative proportions. Consequently, in this domain, the results of animal experiment are not necessarily applicable to human physiology.

On account of the close chemical relationship between bile acids and cholesterol, it has been suggested that the bile acids are formed by direct breakdown of cholesterol in the organism. Windaus (12), in the laboratory, succeeded in oxidizing coprostane to cholanic acid ; and in animal experiments Enderlen, Thannhauser, and Jenke (9, 10) found that intravenous injection of cholesterol in colloidal solution produced no increase in the secretion of bile acids, whereas similar injections of allocholesterol led to considerable increase of this secretion. This result is very interesting, but unfortunately the available methods of estimating bile acids (11) are indirect, and afford no information as to the relative distribution of the different acids. On the other hand, the reverse change appears possible, since Wieland (13) succeeded in synthesizing coprostane from cholanic acid. It is also conceivable that both cholesterol and bile acids are synthesized from some common origin by collateral processes.

3. In 1916 H. Wieland and H. Sorge (14) enunciated the 'choleic acid principle'. They found that deoxycholic acid formed stable molecular compounds with the higher fatty acids, e.g. $8C_{24}H_{40}O_4 + C_{18}H_{36}O_2$, with stearic acid.

The choleic acids isolated from bile were a mixture of such stearic, palmitic, and oleic acid compounds. These compounds go unchanged into the salt condition and are very stable. They crystallize well, and their sodium salts are *easily soluble in water.* Besides the fatty acids, they found that many other substances form somewhat similar compounds. Materials which are insoluble, or nearly insoluble in water, such as naphthalene, xylene, strychnine, quinine, cholesterol, camphor, fat, azobenzene, &c., are brought into solution by an aqueous solution of sodium deoxycholate.

This power of uniting with insoluble substances to form soluble products Wieland called the 'choleic acid principle', and he concluded that it had an important function in transporting insoluble substances, such as fat and fatty acids, through the intestinal wall.

Later Wieland (15) synthesized paired acids of deoxycholic acid with glycine and taurine. These did not, however, behave according to the 'choleic acid principle' and yield compounds with fatty acids identical with the naturally-occurring glycocholeic and taurocholeic acids isolated by Wahlgren (16) and Gullbring (17), although the sodium salts of Wieland's synthetic acids could take up small quantities of naphthalene, quinine, cholesterol, and soap. Presumably he had synthesized acids not quite identical in structure with the naturally-occurring paired deoxycholic acids. It is perhaps important, in connexion with cholelithiasis, to note that the anthropo-deoxycholic acid, isolated from human corpse bile, in which it accompanies ordinary deoxycholic acid, does not obey the 'choleic acid principle' (18).

'The choleic acid principle' appears to provide a more satisfactory explanation of intestinal fat absorption [2] than either the theory of particulate absorption or that of the absorption of fats in the form of soluble soaps. Verzâr and Kuthy (19) have shown the latter method to be unlikely, as soaps are unstable at any of the pH values which exist in the gut. They also showed that fatty acids in solution in the paired bile acids were not only stable at these pH values but that the fatty acids in such solutions could easily diffuse through parchment shells.

Though cholesterol is present in bile, the solution is not saturated, and more cholesterol can be taken up. The early observations of Harley and Wakelin Barratt (20), confirmed by Aoyama (21), are interesting. They showed that human gallstones placed in the gall-bladder of dogs had entirely disappeared in six months, provided that no inflammation had been set up.

4. Ox bile has long been known to have a cholagogue action when given by the mouth. The investigations of Neubauer (22) have shown that deoxycholic acid possesses marked cholagogue activity in animals, and also that the keto-acid, dehydrocholic acid $C_{24}H_{36}O_4$ (which can be administered intravenously), is similarly potent. It is very probable that the same action occurs in man, though the question of dosage is still in dispute (23).

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[2] If this choleic acid principle is the sole method of fat absorption, an extraordinarily rapid bile acid circulation must take place.

5. That cholesterol is synthesized has been clearly proved by Gardner and Fox (24, 25), by Thannhauser (26), Beumer and Lehmann (27), Channon (28) and by Randles and Knudson (29).

6. Cholesterol ingested with the food is absorbed by the alimentary canal, but in this respect the metabolism of herbivora appears to differ very markedly from that in carnivora or omnivora. In the herbivora—ox, sheep, horse, and rabbit—Gardner (30, 31) and other workers have clearly shown that cholesterol is never excreted in the faeces of healthy animals; and they were led to the conclusion that, in the metabolism of these animals, cholesterol is strictly conserved. Considerable evidence was brought forward to show that the cholesterol excreted in the bile, including such cholesterol as arises from the breakdown of erythrocytes, is completely reabsorbed—the so-called 'cholesterol cycle'. In such animals any waste of cholesterol must be made up by synthesis. Before this possibility was proved, many attempts were made by Gardner (32) and others to ascertain whether the vegetable sterols (the phytosterols, &c., of plants) could be absorbed and converted into cholesterol, but the results were inconclusive. Since then the discovery of more precise methods of estimation has enabled Schönheimer (33) to demonstrate that plant sterols, ingested in known quantities in the food, are quantitatively excreted, but that on the other hand cholesterol so administered is very rapidly absorbed (24). In herbivora the administration of cholesterol, which is not a normal constituent of their food, leads to toxic effects. Prolonged feeding of this substance to rabbits, as is well known from the work of Anitskchow (35), Chalatow (36, 37), Bailey (38), Schönheimer (39), leads to cholesterol infiltration of the various tissues, the changes in which have been considered to resemble human pathological processes, e.g. atherosclerosis.

In carnivora and omnivora an excretory mechanism appears to exist, so that there is always a quantity of sterol, mainly in the form of cholesterol or coprosterol, excreted in the faeces (40, 41). In man this excretion has been shown by balance experiments to be always greater in quantity than the amount ingested in food (24). In adult man the bulk of the sterol is excreted in the form of coprosterol, though in infants in the milk stage the excretion is pure cholesterol; but in the latter case there is on the average a slight excess of output over intake (25). However, in carnivora there is no doubt that cholesterol is absorbed from the food and reaches the blood-stream in partially esterified form through the lymph (42), though some may enter the portal circulation directly (34, 43). In carnivora and omnivora no one has ever produced by high cholesterol feeding such pathological phenomena as occur in rabbits.

7. In man, in extension of the work of Gardner and co-workers (32, 56) on rabbits and cats, we have shown (44) that the level of the cholesterol content of the plasma, taken fasting (i.e. before breakfast), can be raised or lowered by *sufficiently* prolonged feeding with diets of high or low cholesterol content. Such changes are most marked as regards the cholesterol in ester form; the free cholesterol remains practically constant.

As a result of a single meal, alimentary hyper-cholesterolaemia (in the ordinary accepted sense) does not occur, and there is no obvious connexion between the amount of cholesterol ingested and the cholesterol level of the plasma during digestion. During the digestive process, changes in the cholesterol content of the plasma frequently occur, sometimes as an increase, sometimes a decrease compared with fasting values. Often a marked temporary disturbance of the ester to total ratio is observed. These peculiar changes cannot be explained by the influx of the cholesterol absorbed from the alimentary canal, but must be considered as evidence of an active endogenous metabolism, in which cholesterol takes part, during digestion (44).

The cholesterol content of the 'fasting' plasma varies markedly in different healthy individuals, but is fairly constant for the individual himself. The following table summarizes the results of our own observations (54): the figures represent grammes per 100 grammes of plasma.

| | Total Cholesterol. | | Free Cholesterol. | | Ester Cholesterol. | |
	Average.	Limits of Variation.	Average.	Limits of Variation.	Average.	Limits of Variation.
Male	0·170	0·11–0·22	0·050	0·005–0·082	0·120	0·08–0·14
Female	0·153	0·08–0·23	0·0540	0·020–0·094	0·100	0·054–0·14

The ester cholesterol usually forms from 60 to 70 per cent. of the total cholesterol.

In any investigations of the metabolic processes, e.g. in jaundice, it must be noted that the values of the plasma cholesterol content represent the resultant of many factors, the balance of which determines the plasma cholesterol level at the moment the blood is taken. Amongst these factors should be included the breakdown of erythrocytes or other body cells, the alimentary absorption of cholesterol, the faecal excretion, the biliary secretion, and lastly the possibility of collateral synthesis of cholesterol or cholic acid and their interconversion.

It was thought that evidence as regards the endogenous metabolism of cholesterol might be obtained by studying the variations of plasma cholesterol in disease of the liver and bile passages. It soon became apparent to us, however, that the metabolism was disturbed grossly and in a complex manner in such conditions, but that the one common factor, which could be correlated with these changes, was the occurrence of jaundice.

For some years we have insisted on the importance of the separate estimation of the two forms of cholesterol, the so-called free and ester forms, many earlier investigations having proved of limited value, if not actually misleading, because (a) total cholesterol alone was determined, (b) whole blood instead of plasma or serum was used, (c) colorimetric methods of estimation of doubtful accuracy were employed. This is well illustrated in pregnancy, where we have shown (45) that the hitherto assumed hypercholesterolaemia is irregular in occurrence, but on the other hand a regular cyclical change of the free and ester values is a *constant* phenomenon in the later months of this condition.

The earlier French workers (46) generally believed hypercholesterolaemia

to be a constant feature of cholelithiasis, and a causal factor of the disease. Their observations were added to by many workers, until Campbell (47) showed that hypercholesterolaemia only occurred when the disease was accompanied by jaundice. Such increase of blood-cholesterol has been explained as a simple retention phenomenon, due to the failure of the excretion of the cholesterol of the bile. Fowweather and Collinson (48), however, believe the hypercholesterolaemia to be due to reabsorption of the biliary cholesterol by the gall bladder. Widal, Weill, and Laudat (49), using very rough methods, first noted that the hypercholesterolaemia of jaundice differed from that occurring in nephritis in that in the former there was mainly an increase of free cholesterol. More recently Thannhauser and Schaber (50) found disturbances in the ester total ratio, and noted a sudden fall of ester values, almost to vanishing point in certain cases. This they refer to as 'estersturz'. They thought it due to a failure of esterifying power of the liver cells, the result of parenchymatous damage. Bürger and Habs (51), Stern and Suchantke (52), Adler and Lemmell (53) criticized these authors, and were unable to confirm the occurrence of 'estersturz'. They agree, however, with Thannhauser and Schaber's finding of hypercholesterolaemia in biliary stasis, with a simultaneous occurrence of comparatively low ester values. They regard the hypercholesterolaemia as due to the retention in the blood of the *free* cholesterol normally excreted with the bile, and believe that this suffices to account for the lowering of the ester-total ratio.

Methods.

In our work we have used the method of plasma analysis published by us in 1927 (54), with the addition that the extraction process now employed is a combination of the two methods therein described. The plasma is at once separated off from the corpuscles and run slowly into the alcohol ether mixture ; the precipitated protein, after thorough washing with alcohol and ether, is dissolved in 2 per cent. sodium hydroxide and further extracted as in Fex's method (71). The actual cholesterol estimation is performed, using digitonin, as described in detail. In order to eliminate the disturbing factor of digestion, the blood was almost always taken with the patient in the 'fasting' condition, i. e. before breakfast. Our results are embodied in Tables I and II.

Description and Discussion of Results.

It is important to stress at once the fact that jaundice from biliary obstruction and the actual biliary obstruction are not necessarily contemporaneous, and that the only plain clinical evidence of existing biliary obstruction is the absence of bile pigment from the faeces. For example, if we compare Cases 23 and 24, *both extremely jaundiced* from impaction of a gallstone in the common bile duct, the former had had persistently colourless faeces for a long period, while the latter had occasional periods of normal coloured faeces. The blood cholesterol picture

of the two cases is entirely different. The former showed marked hyper-cholesterolaemia, while the latter did not; so that, even though in the latter case most of the bile was probably retained, the cholesterol picture had not been so disturbed as in the former.

The cases are arbitrarily divided, so that in Table II only those are shown in which the ester total-ratio, in at least one observation, had been below 50 per cent.

In Table I there is evidence of slight hypercholesterolaemia in some cases where there was no obvious jaundice, but the large majority show figures within normal limits. To determine whether there is true hypercholesterolaemia in Cases 7, 8, 12, 15, 17, where the total cholesterol is just above the values we have found (54) in a study of normal individuals, would necessitate a knowledge of the cholesterol level of the individuals during health. In these cases the ester values alone appear to be somewhat raised.

In all the cases in Table II, failure of bile flow into the intestine had been known to occur, and jaundice had been present in all cases except 18 and 29. Examination of this table reveals two different types of change in the blood cholesterol picture (

(a) On establishment of biliary obstruction, there soon appears a lowering of cholesterol ester content of the plasma, almost to vanishing point in some cases, and at the same time the free cholesterol may be normal or slightly increased: vide Cases 20, 21, 22, 25, 27, 32, 34, 35. If the biliary obstruction is relieved, the picture returns quickly to normal, as in Cases 21, 22, 27.

(b) If absolute biliary obstruction persists, a true hypercholesterolaemia ensues, with a low ester/total ratio of 30 to 50 per cent.

However, the table reveals other significant facts. Cases 18 and 29, in which bile was draining from a fistula, in one case for a short period, in the other for six months, show the first effect described above. Here there was no bile stasis at all, but there was an absence of bile from the intestine. This absence of bile from the intestine occurs both in cases of biliary obstruction and in cases of external biliary fistula; further, it is the only important change common to the two types of case, and consequently it must be considered as the probable cause of the changes of the blood picture of the first type.

Case 21, during a period of transient jaundice, with clay-coloured stools, was treated with deoxycholic and dehydrocholic acids, with the result that in three days, with the re-establishment of the bile flowing into the intestine, the choles-terol ester content of the plasma increased from 0·0023 per cent. to 0·1336 per cent. The rapidity of the return to normal is very striking.

Case 29 shows also a definite increase of free cholesterol over normal values. Here, despite the loss of bile, with its cholesterol, through an external fistula, there is still a hypercholesterolaemia as regards the free form, though there was no retention of bile.

True hypercholesterolaemia of high degree, involving both forms of choles-terol, is seen in Cases 23, 30, and 32, where the biliary obstruction had been

complete for a considerable period. It is of course possible that this second type of change commences at quite an early date and influences, or even partially masks, the early changes in the cholesterol picture.

Cases 1, 2, 3, and 14, all except the last one being post-operative findings, show an almost complete absence of free cholesterol from the plasma, a condition which we have noted before in three healthy men. Our clinical data do not allow us to draw any conclusions at present from these results.

In discussing these findings it seems to us wisest to consider the two types of change separately: (i) to attempt to explain the tendency to 'estersturz' in early biliary obstruction and (ii) to consider the later occurring increase of both forms of cholesterol towards gross hypercholesterolaemia.

(i) The previous workers, Thannhauser and Schaber (50), Bürger and Habs (51), Stern and Suchantke (52), Adler and Lemmell (53), were all somewhat obsessed with the idea of demonstrating phenomena of utility for the finer diagnosis of liver diseases or for the estimation of the degree of liver efficiency. Thannhauser and Schaber, in explaining 'estersturz' as due to loss of esterifying power of damaged liver cells (the whole assumption being quite unsupported), have ignored the consequences of absence of bile from the intestine. Bürger and Habs and also Stern and Suchantke did not accept this hypothesis but considered the estervanishing as unproven, and that there only occurs such a diminution of ester/total ratio as is explicable by retention in the blood of biliary cholesterol, which consists mainly of the free form. Here again the intestinal conditions are neglected. We see, too, that Fowweather and Collinson's theory (48) is quite inadequate, as it cannot account at all for the diminution of ester values in the plasma to below normal; their argument is, however, unsound for other reasons, for they suggest that the power of the gall-bladder for absorbing cholesterol back into the blood stream is shown by the effects of cholecystectomy in reducing hypercholesterolaemia, while ignoring completely whether any happening, e. g. jaundice, in the previous history of the cases, could account for the precholecystectomy figures.

Absence of bile from the intestine, it is known, leads to failure of the absorption of both fat and sterols, and in, for example, Fränkel and Brugsch's (55) work it was shown that sometimes 100 per cent. of the fat ingested could be recovered from the faeces. Surely this failure of fat absorption must be significant and must be correlated closely with the diminution of the cholesterol ester in the plasma. We have seen that by whatever means the bile is deviated from the intestine, whether by obstruction with biliary stasis or by obstruction without bile stasis (the bile flowing away freely through an external fistula) the phenomenon of estervanishing tends to occur. Further, in case 21, the re-establishment of normal biliary flow, together with administration of bile acids, led to the immediate return to normal of the cholesterol ester content of the plasma. These observations might also suggest that normally the ester cholesterol represents that part of the plasma cholesterol which has originated from the alimentary absorption. A previously published (44) experiment of ours is

interesting. An individual who was fed on a sterol-free diet for seven days showed a diminution of plasma ester cholesterol from 0·065 per cent. to 0·032 per cent. but only a small diminution of the free form. Of course, in such a feeding experiment, cholesterol is still flowing into the intestine with the bile and is probably reabsorbed (the cholesterol cycle). The fate of biliary cholesterol and ingested cholesterol in the intestines cannot be distinguished.

Two ways of explaining the tendency to 'estersturz' suggest themselves. One hypothesis is that, in the absence of bile from the intestine, in accordance with Wielands 'choleic acid principle' no cholesterol is absorbed from the intestine, and the absence of such cholesterol, which would have been absorbed mainly in the ester form, gives rise to the same effect as maintenance on a sterol-free diet. The alternative hypothesis is that the failure of fat absorption is the more important factor in the disappearance of ester cholesterol from the blood. With the absence of fat intake from the intestine, the body perhaps utilizes immediately the fatty acid combined with the cholesterol of the plasma—a de-esterification. Such an explanation is suggested by case 29, where, with the absence of bile from the intestine and also the absence of bile stasis (assuming that the latter could account for hypercholesterolaemia by retention), the *total* cholesterol figure is normal, though the ester value is low and the free high. Such an explanation might also be applicable to the lowering of the ester/total ratio in pregnancy, where possibly a rapid removal of the fat or fatty acids from the blood might occur and this account for the facts observed.

In case 21 there was in three days a large increase of cholesterol ester in the plasma immediately after the re-establishment of normal biliary flow. In this period, calculating the plasma volume from the patient's weight, there was an increase of about 4·3 grm. of cholesterol as ester in the whole plasma, which is an increase of about 1·4 grm. of cholesterol per day, a figure which, as we shall see later, is much larger than the probable average daily absorption of cholesterol in normal individuals. It is difficult to explain such an increased rate of absorption unless the bile, suddenly poured into the intestine after a period of what was equivalent to fat starvation, possessed a markedly increased dissolving power for cholesterol and fatty acids. Perhaps under such conditions of fat starvation the percentage of choleic acids is less than normal, i.e. a smaller proportion of the deoxycholic acid is in combination with fatty acids, and the bile, enriched as it was in this case by deoxycholic acid given by mouth, might have possessed cholesterol dissolving capacity in excess of normal. Further, the sudden inflow of fatty acid from the intestine might lead to mobilization of tissue cholesterol in order to aid the transportation of fat in the blood.

In making these suggestions, which we think are more in accord with modern physiological knowledge, we at present only consider them as working hypotheses on which to base further investigation.

(ii) Consideration of the later occurring hypercholesterolaemia presents certain difficulties for, in spite of the persistent failure of fat absorption, cholesterol

in *both* forms piles up in the plasma, and though the ester form lags behind the free its value can still reach a high figure. If the hypercholesterolaemia is due solely to retention of the free cholesterol of the bile, it might be suggested that some of the retained cholesterol is esterified by the mobilization of fat from fat depots. This utilization of the body stores of fat probably also liberates the associated cholesterol in these stores, and this possibility has been suggested as an explanation of the hypercholesterolaemia which occurs in starving animals (56).[3] However, the hypercholesterolaemia, which occurs in biliary obstruction, is generally believed to be due to cholesterol retention; but when we consider that, in bile stasis, there is probably at the same time failure of alimentary cholesterol absorption, it is by no means obvious that cholesterol retention is not balanced by this failure. In herbivora the cholesterol cycle is almost complete, but in man the average rate of the alimentary absorption is probably less than the rate of the biliary secretion of cholesterol. If we consider the result of the twenty-six balance experiments reported by Gardner and Fox (24), which were done on six-day periods, we find that the average excess of output over intake was about 0·31 grm. per day. It is perhaps difficult, at first sight, to accept this average of wide variations as a truly significant figure, but, of course, such an average figure only applies if the balance is considered over many days. In these experiments, if we obtain the average of the balances of all the experiments, for each individual in turn, the gross variations promptly disappear and the averages of the individuals are, with two exceptions, quite close to the general mean. A figure can also be obtained for the average biliary excretion of cholesterol; from the data collected in Fox's (57) paper this average is about 0·37 grm. per day. If we, temporarily, assume that there is no appreciable quantity of cholesterol in the intestine other than that ingested, or of biliary origin, and that none is decomposed therein, then the figures just given enable us to calculate the daily average absorption of cholesterol from the gut: for, if the daily output exceeds the intake by 0·31 grm. per day, and if 0·37 grm. of cholesterol enters the intestine with the bile in that time, then clearly 0·06 grm. of cholesterol must be absorbed per day. These assumptions are, however, only made for simplicity of calculation, and require further consideration. There is no evidence that cholesterol is synthesized in the gut by bacteria, or that the substance of the bacteria contains any cholesterol or coprosterol (indeed if any sterol were present it would probably belong to the fungus group, as ergosterol); there is equally no evidence that cholesterol is decomposed in the intestine, so that all these factors can be neglected. However, since Voit's (58) classical experiment on the production of faeces-like material, containing fat, in an isolated loop of small intestine, evidence has been accumulated by Sperry (59), Bürger and Oeter (60), and by Beumer and Hepner (61) that fat and cholesterol are excreted into the intestinal lumen. Sperry (59), experimenting with dogs fed on 'lipid' free diet, has shown that

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[3] In man we have not succeeded in demonstrating this change, but as the experiments were done by blood analyses on individuals, starving as a result of carcinoma of the oesophagus, the conditions are not exactly comparable.

the intestinal excretion of fat and cholesterol is greater in a bile fistula animal than in the normal, and he explains this excess as due to the failure of re-absorption of these materials in the absence of bile. His suggestion that this intestinal excretion may be due to desquamation is improbable, since the amount of material desquamated, which would be required to produce the cholesterol found, would be of the order of 100 grm. per day; and further such a theory would not explain the complete absence of cholesterol in the faeces of herbivorous animals such as horse, rabbit, cow, sheep, feeding naturally in the open. That an excretion of cholesterol by the gut may occur is further supported by Schönheimer (62) and co-workers who have found a hydrogenized sterol in the excretion of a large intestine which had been isolated by the performance of a complete ileostomy. The result of such an excretion would be that the figure of daily absorption of cholesterol, as calculated above, must be increased by an amount equal to that excreted by the intestinal wall, in order to preserve the known balance (of output over intake). If biliary stasis then ensues, it is very probable, as Sperry (59) assumes for his dogs, that re-absorption does not occur, and that there must result a faecal excretion of the body cholesterol. The bile fistula dog, weighing about 10 kilos, on a lipid free diet, excreted, on the average, 1·6 grm. of unsaponifiable matter per week, and of this 35 to 40 per cent. was cholesterol: this would be an excretion approaching 0·1 grm. of cholesterol per day. If a 10 kilos dog can excrete 0·1 grm. of cholesterol a day, it would only be necessary to assume that man has an intestinal excretion of three times that figure for the whole theory of hypercholesterolaemia as due to the retention of bile cholesterol to fail completely, since the intestines would excrete (without reabsorption being able to occur) as much cholesterol as would be retained by biliary stasis. It might be possible to obtain further evidence on this problem by performing balance experiments on patients with jaundice, or with a complete biliary fistula, by feeding on a sterol free diet. Such experiments would not be easy owing to the constipation generally shown by such cases. However, we are attacking this problem.

We do think that these speculations are based on sufficient experimental data to justify our doubting the validity of any hypothesis, which explains the hypercholesterolaemia occurring in biliary obstruction as produced by cholesterol retention; and further we feel that no satisfactory theory can be evolved without consideration of the cessation of bile acid production which occurs, and its effects on sterol metabolism.

Clinical Discussion.

We do not propose to discuss here, in detail, the aetiology of cholelithiasis, but a study of available facts concerning cholesterol metabolism makes it very evident that some of our therapeutic methods are unsoundly based. It is commonly held that both high fat feeding and hypercholesterolaemia are factors which

may influence the formation of gallstones and, as a consequence, cases of chole-lithiasis are often treated with diets of low fat content. One authority (63), on the supposition that hypercholesterolaemia is present in pregnancy, goes so far as to suggest that reduction of fat intake should always be observed in the later months of pregnancy. The evidence which is offered to justify these notions is hardly convincing, and rests mostly on analyses of fistula bile taken during feeding experiments or during the ingestion or injection of cholesterol. Actually the normal variations of the cholesterol content of the bile are so considerable that most of the experimental results obtained under these different conditions come within normal limits. We consider that, at present, no one has succeeded in demonstrating that diets of different cholesterol content have any effect on the level of the bile cholesterol (see also Whipple (64), Beumer and Hepner (61)) That hypercholesterolaemia influences the bile cholesterol is so far a pure assumption, though Bacmeister and Havers (65) thought that they had demon-strated in a dog a *diminution* of the bile cholesterol during pregnancy. In human beings, hypercholesterolaemia *sometimes* occurs during pregnancy, but in all cases there is a large increase of free cholesterol and a corresponding decrease of ester cholesterol for a relatively short period in the later months, the return to normal beginning before parturition. An attempt (66) has been made to show, by examination of post-mortem records, that in granular kidney there is an increase over normal of the incidence of cholelithiasis, but as this type of renal disease is not that in which hypercholesterolaemia occurs, the figures are of little value. We have repeated this investigation on cases of sub-acute parenchymatous nephritis, where one can safely assume that hyperchole-sterolaemia of high degree had been present in the majority of cases for long periods, and we could find no evidence that *such* hypercholesterolaemia led to the formation of gall-stones.

For many years an opposite method of treatment by feeding with fat, oil, or cream has been advocated, and Hurst (63) admits that olive oil sometimes relieves the dyspepsia associated with gall-bladder disease. As Goldschmidt (67) and Dreyfus (68) have also pointed out, we can no longer criticize such a form of treatment on the ground that fat feeding influences the cholesterol content of the bile; and the advantages of such a treatment, which provides additional physiological stimulus to gall-bladder contraction and emptying, should be seriously considered. On the other hand, reduction of the fat intake, by with-drawal of egg-yolk and butter, for example, removes this stimulus (69), thereby promoting gall-bladder stasis. No amount of theorizing about the amount of cholesterol in the bile can possibly justify this latter.

Another method of increasing bile flow is by using deoxycholic and de-hydrocholic acids, the choleretic action of which has been studied particularly by Neubauer (22). The term choleresis has been suggested by Brugsch and Horsters (70) to denote increase of the hepatic bile flow, the word cholagogue being retained for increase of bile flow resulting from gall-bladder contraction. Excepting where there is complete, or almost complete, biliary obstruction, there

seems to be no danger in using these bile acids—even in cholelithiasis. It would appear that in the majority of patients suffering from gall-stones the occurrence of symptoms is due more to associated inflammation than to the presence of calculi, and, from our own results, we are not impressed by the possibility that administration of these bile acids might precipitate an attack of biliary colic. Our efforts to treat cholecystitis, whether acute or chronic, with or without calculi, by the use of choleretics has given promising results, and the method seems worthy of further investigation. As examples we may quote briefly two of our cases:

Male, aged 55 (case 17). History of pain in right hypochondrium and lumbar region and right arm for two years, becoming worse two weeks before admission to hospital. Occasional nausea with pain; never jaundiced. Tender on deep palpation over gall-bladder. 24.10.29, cholecystography (intravenous technique)—no shadow seen. 3.11.29, 5 cc. 20 per cent. dehydrocholic acid (Decholin) intravenously, followed by 10 cc. on each of the next two days. 7.11.29, cholecystography revealed normal but large gall-bladder. Pain and tenderness over gall-bladder vanished and has not recurred.

Male, aged 59. Paratyphoid B. infection. At the end of the second week signs of acute cholecystitis appeared, there was slight yellowing of the conjunctivae but no bile pigment in the urine. Pain and tenderness increased for four days and he was then treated with deoxycholic acid (Degalol) 4 tablets t.d.s. for four days, at the end of which time the acute symptoms had completely subsided. A slight recurrence of tenderness four weeks later was treated successfully in the same way.

The successful use of deoxycholic acid has led us to consider the possibility that the composition of bile, as regards its relative content of the different acids, may be important in the production of gall-stones. It will be recalled that in human bile there are two dihydroxy-cholanic acids, deoxycholic and anthropodeoxycholic acids, and that Wieland's 'choleic acid principle' applies only to the former. In corpse bile, analysed by Wieland (18), it was found that the former acid was present in much greater relative proportion than in ox bile, and it seems very possible that the amount of this acid secreted is the main factor in keeping biliary cholesterol in solution.

Summary.

1. An account is given of the close chemical relationship of cholesterol and the bile acids, and of the importance of considering their activities together as members of one metabolic group.

2. The importance of Wieland's 'choleic acid principle' in relation to the alimentary absorption of cholesterol and fats is described and its application to some of the problems of biliary disease.

3. The changes in cholesterol metabolism, as shown by the cholesterol content of the plasma, which occur in biliary and liver disease are of two kinds:

(*a*) An initial sudden fall of ester cholesterol values, the free cholesterol remaining almost unchanged. This occurs in jaundice from obstruction and

also in cases of complete external biliary fistula. This change is probably due to the absence of bile from the intestine and to the consequent failure of absorption of cholesterol and fat from the gut. If the obstruction is relieved the return to normal is very rapid.

(*b*) When the biliary obstruction is complete for a long period, with the accompaniment of intense jaundice, the first change is replaced by a slowly developing hypercholesterolaemia. This may reach very high values but the percentage of the total cholesterol as ester is still below normal, i.e. below 50 per cent.—the normal being 60 to 70 per cent. The usual theory that this change is due to retention in the blood of the cholesterol from the bile is quite inadequate.

4. Hypercholesterolaemia does not occur in uncomplicated cholelithiasis.

5. There is no evidence that the cholesterol content of the food influences the cholesterol content of the bile or has any relation to the formation of gallstones.

The marked hypercholesterolaemia, which occurs in some forms of nephritis, also does not lead to any increased incidence of cholelithiasis.

Restriction of fat intake in cholelithiasis is unjustifiable, and is more likely to be harmful than beneficial.

6. In deoxycholic and dehydrocholic acids we possess true bile-driving agents, i.e. substances which increase the hepatic biliary flow. Such ' choleretic' action can be of considerable service in inflammatory conditions of the biliary tract.

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TABLE I.

TABLE I.

Case No.	Age.	Sex.	Disease.	Presence of Jaundice.	Duration of Jaundice.	Date.	Cholesterol per 100 grm. Plasma.			% of total Cholesterol as Ester.	Remarks.
							Free.	Ester.	Total.		
1	55	♂	Perforative cholecystitis, solitary gallstone	Nil	—	1.4.25	Nil	0·1234	0·1234	100	
2	64	♀	Cholelithiasis	,,	—	1.4.25	0·0013	0·1181	0·1194	99·2	Cholecystostomy 5 weeks previously which was followed by free bile drainage for 2 weeks
3	51	♀	Solitary small gallstone	,,	—	6.4.25	Nil	0·1525	0·1525	100	5 days after partial cholecystectomy
4	60	♂	Cholelithiasis	+	—	8.7.26	0·0798	0·1085	0·1883	57·7	Plasma pigmented. Stones contained 85 % cholesterol
5	57	♀	,,	Nil	—	12.7.26	0·0811	0·0897	0·1708	59·5	
6	53	♀	,,	,,	—	8 1 27	0·0346	0·0864	0·1210	71·4	Cholecystostomy 10.1.27. Stones contained 94·1 % cholesterol
					—	8.2.27	0·0632	0·1307	0·1939	67·4	Very little bile drainage after operation
7	50	♀	,,	,,	—	24.1.27	0·0791	0·1757	0·2548	69·8	Cholecystostomy 27.1.27. Small stones with 84·7 % cholesterol
					—	16.2.27	0·0859	0·1791	0·2650	67·5	Bile drainage ceased 9.2.27
8	53	♀	,,	?	—	23.4.27	0·0850	0·1919	0·2769	69·3	Cholecystectomy 28.4.27. Stones with 84·3 % cholesterol
					—	20.5.27	0·0727	0·0767	0·1494	51·3	
9	60	♂	,,	Nil	—	23.4.27	0·0704	0·0814	0·1518	53·6	
10	50	♀	,,	—	!	27.4.28	0·0818	0·0864	0·1682	51·3	Cholecystectomy 28.4.27. Stones with 90·2 % cholesterol
						4.5.28	0·0657	0·0733	0·1390	52·7	
11	37	♀	,,	+ (Fading)	—	2.5.27	0·1161	0·1288	0·2444	52·0	Cholecystostomy 3 5 27. Stones with 68·5 % cholesterol
12	53	♀	,,	V. slight Nil	—	10.5.27	0·0855	0·1351	0·2206	61·7	} Draining bile freely
					—	17.5.27	0·0728	0·1370	0·2098	65·3	
13	48	♂	,,	(Fading) + Slight	—	18.8.27	0·0839	0·1513	0·2352	64·4	
					—	1.11.29	0·0497	0·1194	0·1693	70·6	
14	40	♂	? ,,	+	3 days	18.4.28	0·0070	0·1003	0·1073	93·5	Stones contained 84·0 % cholesterol
15	67	♀	,,	V. slight Nil	—	15.2 29	0·0849	0·1770	0·2619	67·6	Stools light in colour
					—	27.2.29	0·0878	0·1685	0·2363	65·6	
16	38	♀	Perforation of gallbladder	Nil	—	3.6.24	0·0405	0·0694	0·1099	62·2	
17	55	♂	Cholecystitis	,,	—	20.9.29	0·0703	0·1859	0·2561	72·6	
						11.11.29	—	—	0·2467		

TABLE II.

Case No.	Age.	Sex.	Disease.	Presence of Jaundice.	Duration of Jaundice.	Date.	Free.	Ester.	Total.	% of total Cholesterol as Ester.	Remarks
18	39	♂	Cholelithiasis	Nil	—	17.7.26 27.7.26 5.8.26	0·0777 0·0790 0·0620	0·1128 0·0520 0·1104	0·1905 0·1310 0·1706	59·3 39·9 64·8	Cholecystotomy 20.7.26 } Draining bile freely
19	42	♂	,,	Not obviously jaundiced but urine contained bile pigment	—	13.12.26	0·0881	0·0650	0·1531	42·4	Cholecystotomy 14.12.26. One stone was felt in common bile duct. Stone contained 70 % cholesterol
20	63	♀	,,	Jaundice had nearly faded	—	24.1.27	0·0807	0·0123	0·0930	13·2	Cholecystectomy 28.1.27. No stones found. Previous cholecystostomy in 1924
21	62	♂	,,	+ +	— —	29.12.27 3.1.28	0·0674 0·0846	0·0048 0·0023	0·0727 0·0869	6·65 2·65	Gallstones showed clearly by X-ray. Deoxycholic acid from 29.12.27 to 3.1.28. Faeces pale
				0	—	6.1.28	0·0817	0·1334	0·2152	62·6	Dehydrocholic acid daily, intravenously, 3.1.28 to 6.1.28. Faeces normal in colour
				0	—	6.2.28	0·0901	0·1725	0·2626	65·0	
22	44	♂	N.A.B. jaundice	++ Nil	2 weeks —	1.6.28 3.7.28	0·1130 0·0815	0·0202 0·1073	0·1332 0·1888	15·1 56·9	
23	71	♂	Impacted stone in common bile duct	+++	18 months	30.6.28	0·3584	0·2391	0·5975	40·6	Faeces clay coloured
24	31	♀	Impacted stone in common bile duct	+++	10 months	11.7.28	0·0920	0·0671	0·1600	41·9	The faeces were occasionally normal in colour. The biliary obstruction must have been intermittent
25	40	♀	Acute yellow atrophy	++	—	1.11.28	0·0709	0·0234	0·0943	24·2	

No.	Age	Sex	Diagnosis		Duration	Date					Remarks
26	32	♀	Cholelithiasis	Nil	—	22.11.28	0·0751	0·0908	0·1659	54·7	Gallstones shown by plain X-ray. Patient having occasional attacks of colic without noticeable jaundice
				,,	—	12.12.28	0·1066	0·0949	0·2015	47·1	
				,,	—	11.1.29	0·0796	0·0954	0·1750	54·5	
27	70	♀	,,	Trace	A few months	19.12.28	0·1052	0·0635	0·1687	37·6	Jaundice had almost faded
				Nil		3.12.28	0·0751	0·1032	0·1783	57·8	After treatment with deoxycholic and dehydrocholic acids
28	44	♂	Chronic pancreatitis	+	4 days	22.1.29	0·1764	0·1114	0·2878	39·6	Wassermann ++. Cholecysto-stomy performed later; diagnosed as carcinoma pancreas but complete recovery ensued – presumably pancreatitis
29	60	♂	Biliary fistula after operation for acute cholecystitis	Nil	—	15.3.29	0·1248	0·0091	0·1339	6·8	Biliary fistula during previous 6 months. Stools quite clay coloured
				,,	—	18.4.28	0·0602	0·0823	0·1425	57·5	Fistula now closed and stools normal
30	68	♂	?	++	—	18.4.24	0·2086	0·2105	0·4192	50·3	Duration of jaundice unknown. Diagnosis uncertain. Large abdominal tumour below liver
31	50	♂	N.A.B. jaundice	+	4 weeks	28.6.29	0·0982	0·0651	0·1633	39·8	
32	60	♀	Cholelithiasis carcinoma head of pancreas and at neck of gall bladder	++	11 days	28.6.29	0·0829	0·0870	0·1699	51·7	Faeces clay coloured persistently
				++	7 weeks	16.8.29	0·2484	0·1074	0·3559	30·2	
33	77	♂	Carcinoma of pancreas	+++	4 weeks	23.10.29	0·1484	0·1004	0·2448	40·3	Faeces light in colour
34	65	♂	Secondary carcinoma liver and gall-bladder	++	2 months	12.11.29	0·1481	0·0324	0·1805	17·9	Faeces slightly pigmented
				++	—	20.11.29	0·1544	0·0279	0·1823	15·3	Faeces quite clay coloured
35	63	♂	Gummata of liver	++	—	4.12.29	0·1407	0·0710	0·2117	33·5	Wassermann positive
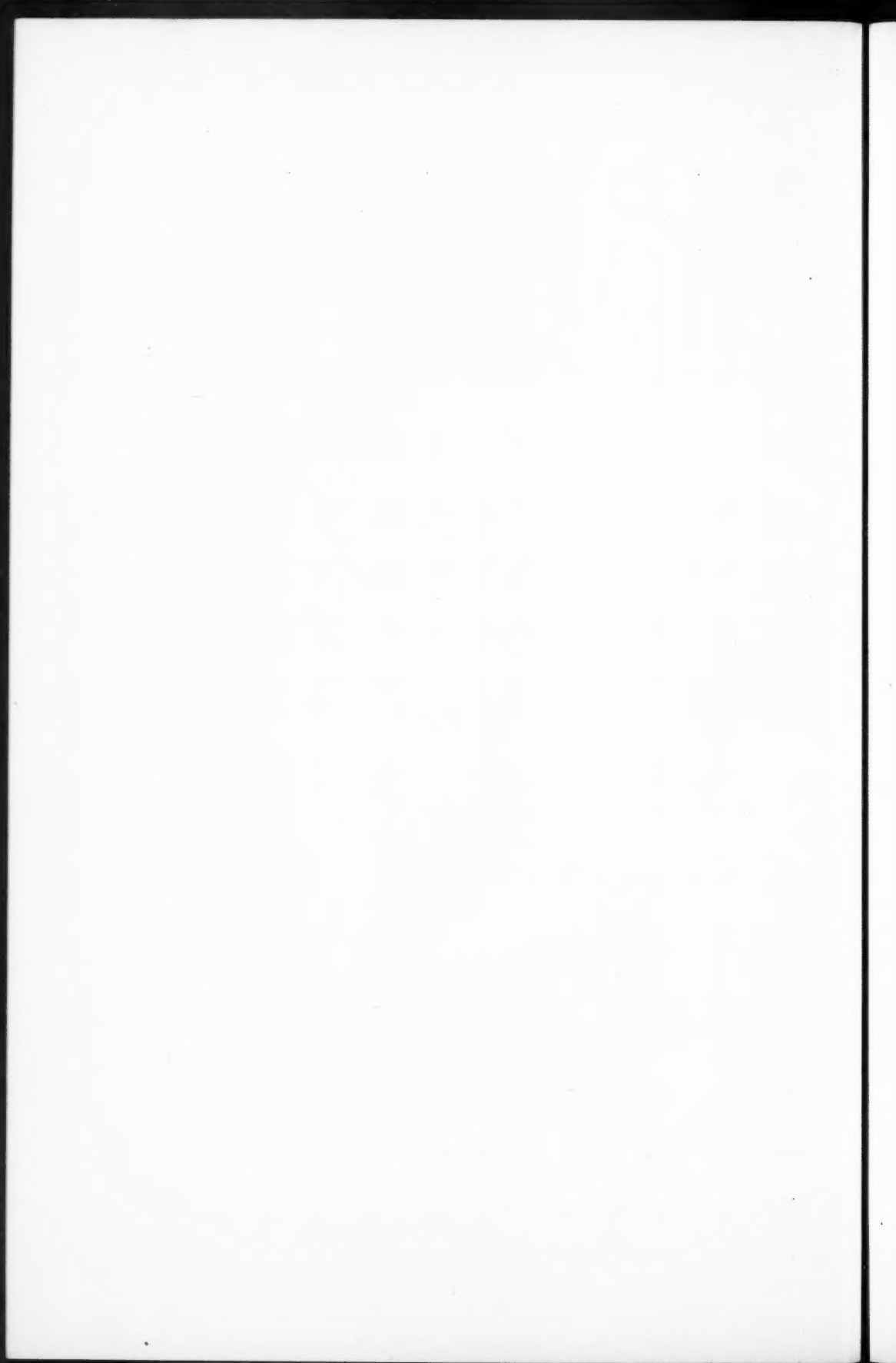
THE ACTION OF ADENOSINE UPON THE HUMAN HEART [1]

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With Plate 24

THE following observations were made in order to ascertain the effects of adenosine upon the human heart and, in particular, to determine whether it can restore the normal cardiac rhythm in cases of auricular fibrillation.

Originally prepared from yeast nucleic acid (2), adenosine is a pyrimidine nucleoside which, in contrast with certain other nucleic acid derivatives, is readily deaminated and biologically active. Drury and Szent-Györgyi (1) have investigated the biological actions of adenosine and adenylic acid in the experimental animal. Both substances 'slow the rate of beating, impair conduction from auricle to ventricle, and arrest experimentally produced auricular fibrillation ; they shorten the absolute refractory period of and improve slowed conduction in the auricle due to high rates of beating. They lower general arterial pressure. This is due in part to the cardiac slowing and in part to a general arterial dilatation. They dilate the coronary vessels and inhibit intestinal movements '. Thannhauser and Bommes (3) had previously shown that, in contradistinction to adenine, adenosine, injected subcutaneously in man, is not toxic. Thannhauser and Schaber (4), who gave 1 grm. adenosine intramuscularly in an experimental study of nuclein metabolism, indicated that intravenous injection was preferable, but do not specifically state that they gave adenosine intravenously.

The adenosine that we employed was obtained from British Drug Houses Ltd. Dissolved in 6 per cent. gum saline solution it was injected subcutaneously into the right forearm or intravenously at the right elbow of the recumbent patient. Continuous electrocardiograms by derivation II or a direct chest lead, with simultaneous record of the left brachial pulse, were taken on films. The injection period, which varied from 2 to 67 seconds, was indicated by an electric signal. In certain cases the pulse-rate was recorded by means of Mackenzie's polygraph.

Subcutaneous injection in doses up to 150 mg. was never accompanied or followed by any local reaction, nor did any patient ever complain of symptoms referable to the injection. After adenosine was given intravenously in doses

[1] Received June 2, 1930.

of 0·5–1 mg. no unpleasant effects were experienced. Immediately after
5–7·5 mg. intravenously the patient may feel ' light-headed' momentarily ; after
7·5 mg. intravenously one patient felt a momentary sensation of tingling in
the head which he raised from the couch, and he became slightly restless.
Fifty mg. intravenously was neither accompanied nor followed by any un-
pleasant effects in one case, but in another the breathing became deeper and
more rapid, the patient became restless, felt breathless, and experienced a sense
of constriction of the chest.   The patient to whom 100 mg. was given felt faint
and giddy, she became restless and pallid, and the breathing became faster and
more shallow.   All these symptoms and signs were uniformly transient and
vanished after a few seconds, certainly within half a minute.

Effects on the Heart Beating with Normal Rhythm.

The subcutaneous injection of 100–150 mg. adenosine did not cause any
slowing of the heart's rate.   During a period of 2 hours 40 minutes after sub-
cutaneous injection of 100 mg. adenosine in a man aged 62, the maximal pulse-
period was only 0·84 second 12 minutes after the injection, the corresponding
pre-injection figure having been 0·80 second.   Again, in a man aged 59, the
pulse-rate remained steadily at 87–88 per minute for 8 minutes 40 seconds after
the subcutaneous injection of 100 mg. adenosine began.

Intravenous injections were speedily followed by pronounced effects. After
7·5 mg. adenosine intravenously in a man aged 52 there was sudden cardiac
slowing from the 20th to the 26th second after the injection began (Fig. 1), the
duration of consecutive inter-ventricular periods being 0·80, 0·78, 0·80, 0·86,
1·80, 1·72, 1·56, 1·44, 0·68, 0·72, 0·72, 0·68 seconds.   The transient slowing was
succeeded by mild acceleration.   Owing to transient somatic tremor the P–R
interval, which was 0·16 second prior to the injection, could not be determined
during the period of cardiac slowing.   The ventricular complexes remained
unaltered.

After 50 mg. intravenously the effects were more obvious.   A man
aged 59, in whom 100 mg. adenosine subcutaneously had failed to evoke any
recognizable effect, received 50 mg. adenosine intravenously during a period of
50 seconds.   The pulse-rate began to lessen at the 25th second after the in-
jection began ; from the 28th to the 31st second there were dropped beats,
probably due to impaired conduction from auricles to ventricles ; from the 59th
to the 67th second there was gross arrhythmia, with dropped beats and
irregularity of volume of pulse waves (Fig. 2) until the 80th second, followed
by pulsus alternans until the 118th second.   At the 120th second the pulse was
again regular and equal, and it remained so until the record ended two minutes
later.   After a second intravenous injection of 50 mg. adenosine eight days later,
slowing of auricles and ventricles began 25 seconds after the injection started ;
from the 28th to 30th second there was 2 : 1 auriculo-ventricular heart block
without deformity of the ventricular complexes (Fig. 3), and the 2 : 1 block

recurred from the 59th to the 61st second. Thereafter the cardiac retardation began to pass off and the pre-injection rate was regained at the 75th second (Fig. 4).

Effects on the Heart Presenting Auricular Fibrillation.

In three cases of auricular fibrillation adenosine was injected subcutaneously in doses of 50–150 mg. The fibrillation persisted unchanged during periods of 7, 11, and 45 minutes respectively. In one of these cases, a male aged 45, who was under the care of Dr. Goodall, there was slight ventricular slowing, perhaps more apparent than real, seven minutes after the injection.

Given intravenously in five cases adenosine, in doses of 0·5–100 mg., failed to influence the auricular fibrillation. In contradistinction to the changes that may ensue after administration of quinidine, the auricular deflexions did not become slower and the ventricular irregularity persisted. In Case 1, a man aged 41, there was slight ventricular slowing from the 50th to the 70th second after 5 mg., but none after 0·5 mg. or 1 mg. In Case 2, a man aged 45, there was ventricular slowing from the 25th to the 30th second after 5 mg., but none after 2·5 mg. In Case 3, a man aged 64, the ventricles were not retarded after 5 mg., nor again after 7·5 mg. In Case 4, a woman aged 44 suffering from mitral and tricuspid stenosis, there was ventricular slowing from the 25th to the 35th second after 7·5 mg., the duration of consecutive inter-ventricular periods being 0·48, 0·60, 0·66, 0·64, 0·88, 2·26, 1·52, 1·38, 1·30, 0·96, 0·80, 0·90, 0·64, 0·46, 0·52 seconds. In Case 5, a woman aged 44 affected with mitral stenosis and toxic goitre, 50 mg. adenosine were injected during a period of 67 seconds. Pronounced ventricular slowing began 80 seconds after the start of the injection and passed off gradually 20 seconds later. While the ventricles were being retarded the auricular deflexions became larger ; T, which had been isoelectric, became an upright deflexion of 5–7 mm. from the 83rd to the 109th second and ventricular extra-systoles occurred. In the same case, with an average pre-injection inter-ventricular period of 0·35 second, 100 mg. were given intravenously during a period of 34 seconds. Ventricular slowing began 32 seconds after the start of the injection and persisted until the 70th second ; it was maximal from the 34th to the 55th second, the duration of successive inter-ventricular periods being 1·60, 0·52, 0·68, 1·36, 1·16, 1·20, 0·88 seconds. During the period of ventricular slowing two extra-systoles occurred. T, which was isoelectric when the observation began, again became an upright deflexion. Its height was 1·5 mm. 30 seconds from the start of the injection ; it attained a maximum of 3 mm. at the 37th second, then declining to 2 mm. at the 65th second and 1·5 mm. at the 75th second. From the 80th second onwards T was again isoelectric. The form of the initial ventricular complex was unchanged throughout ; the R–T period, when recognizable, was consistently of 0·28 second duration.

Adenosine has thus a prompt but evanescent action upon the human heart. In man the subcutaneous injection of 150 mg. was not followed by any

recognizable effect upon the heart or blood-pressure. Larger doses might perhaps be effective, because the subcutaneous injection of adenosine causes heart-block in the experimental animal, the effect being maximal in about five minutes and passing off gradually about one hour later (1). But after intravenous injection of 5–100 mg. we observed prompt effects in six of our seven cases. There was slowing of the whole heart in two cases with a sinus rhythm, and of the ventricles in four cases of auricular fibrillation. In five cases the slowing began 20–32 seconds after the start of the injection; in one fibrillator the onset of ventricular slowing was delayed until the 50th second after 5 mg.; in another fibrillator the ventricular rate remained unchanged after 5 and again after 7·5 mg. The slowing was always extremely transient and thus comparable to that developing in the dog within 10–15 seconds and passing off about 60 seconds later. Drury and Szent-Györgyi (1) showed that this effect is not due to vagal stimulation. After 50 mg. intravenously, one patient presented prompt slowing of the whole heart with transient 2:1 auriculo-ventricular block; a few seconds later, about one minute after the start of the injection, the block recurred. In the cat there is an analogous transient primary bradycardia within 20 seconds and a secondary bradycardia, of vagal origin, starting at about the 50th second and lasting for about 40 seconds (1). As the auriculo-ventricular block is not accompanied by any change in the form or duration of the initial ventricular complex, adenosine does not appear to have any action on the branches of the auriculo-ventricular bundle. Although ammonia is formed by deamination of adenosine the increased amplitude of T observed in one case cannot be regarded as comparable to the alterations in the form and direction of T that may be induced by changes in the acid-base balance. Drury and Szent-Györgyi (1) held that adenosine has no definite influence upon the properties of the ventricular muscle, and state that it is not toxic for experimental animals. But the human heart, particularly when diseased, is not necessarily so tolerant to adenosine as is the heart of the cat or other healthy experimental animal. Indeed, the development of alternation and marked irregularity of the pulse-beats (Fig. 2) points to adenosine having a toxic action upon the human heart.

In dogs with experimentally produced auricular flutter and fibrillation adenosine promptly restored the normal cardiac rhythm (1). No opportunity has yet arisen of attempting to restore the normal cardiac rhythm in a patient presenting auricular flutter. But in each of the fibrillators to whom adenosine was administered the auricular fibrillation persisted, even although the quantity injected was large enough to induce the undesirable effects to which reference has been made.

Summary.

We do not regard adenosine as a useful therapeutic preparation for the treatment of heart disease.

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3. Thannhauser, S. J., and Bommes, A., *Zeitschr. f. physiol. Chem.*, Berlin, 1914, xci. 336.
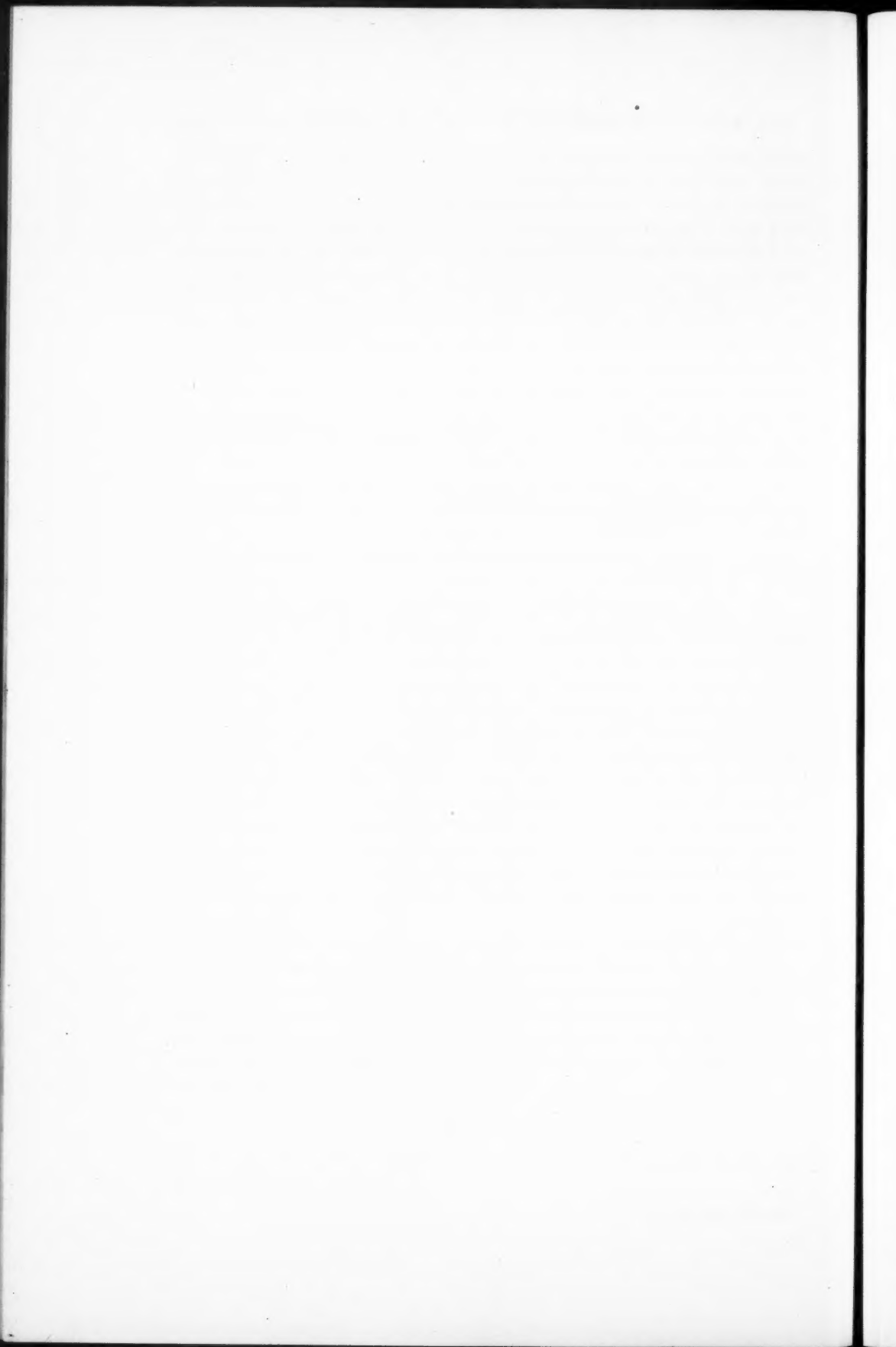4. Thannhauser, S. J., and Schaber, H., *ibid.*, Berlin, 1921, cxv. 170.

DESCRIPTION OF PLATE

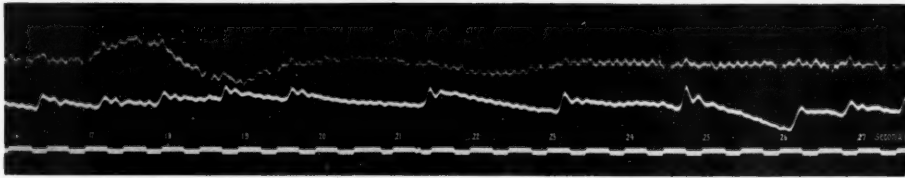PLATE 24, FIG. 1. Electrocardiogram and brachial sphygmogram showing cardiac slowing from the 20th to the 26th second after 7·5 mg. adenosine intravenously in a man with normal cardiac rhythm.
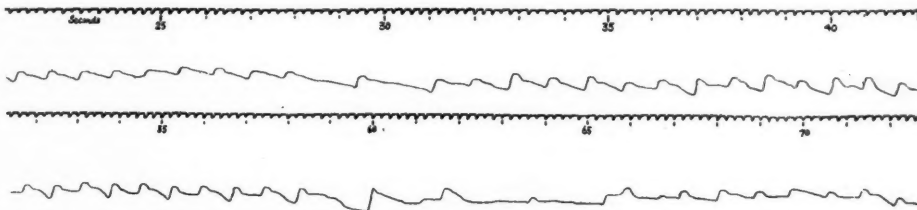
FIG. 2. Primary bradycardia with dropped beats between the 28th and 31st seconds, and secondary bradycardia with marked arrhythmia between the 59th and 67th seconds after 50 mg. adenosine intravenously.
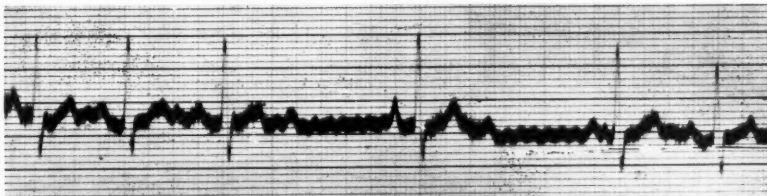
FIG. 3. Transient 2 : 1 auriculo-ventricular block beginning 28 seconds after 50 mg. adenosine intravenously.
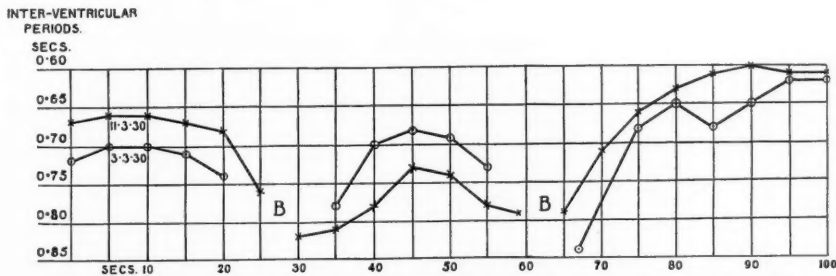
FIG. 4. Two intravenous injections of 50 mg. adenosine in a man with normal cardiac rhythm were followed by a primary and a secondary slowing of the heart, during each of which there was 2 : 1 auriculo-ventricular block indicated by the letter B.

K k

FIG. 1. Electrocardiogram and brachial sphygmogram, showing cardiac slowing from the 20th to the 26th second after 7·5 mg. adenosine intravenously in a man with normal cardiac rhythm.

FIG. 2.   Primary bradycardia with dropped beats between the 28th and 31st seconds, and secondary bradycardia with marked arrhythmia between the 59th and 67th seconds, after 50 mg. adenosine intravenously.

FIG. 3.   Transient 2 : 1 auriculo-ventricular block beginning 28 seconds after 50 mg. adenosine intravenously.

FIG. 4.   Two intravenous injections of 50 mg. adenosine in a man with normal cardiac rhythm were followed by a primary and a secondary slowing of the heart, during each of which there was 2 : 1 auriculo-ventricular block indicated by the letter B.

ACHALASIA OF THE CARDIA[1]

(*So-called Cardiospasm*)

By ARTHUR F. HURST and GEOFFREY W. RAKE.

With Plate 25

History.

DILATATION of the oesophagus without organic obstruction was first described by Purton (30) in 1821 ; the symptoms in his case had been present since childhood, and death occurred at the age of 43. Mayo (23), in 1828, described a case in which death followed exhaustion after symptoms had been present for ten years ; the whole oesophagus except the lowest inch was greatly dilated. Both of these cases were thus reported before Hannay (12), who is generally said to have been the first to recognize the condition, published an account of his case in 1833. A fourth case was added by Rokitansky (34) in 1842, the specimen from which is in the Pathological Museum at Vienna.

In 1866 Wilks (41) showed a specimen, now in Guy's Hospital Museum, before the Pathological Society of London from a man of 74, who had died of pneumonia after suffering from dysphagia all his life. Dr. Rootes of Ross, who sent the specimen to Sir Samuel Wilks, told him that his father, who had looked after the patient since 1812, had taken him forty years before to Sir Astley Cooper, who had passed a bougie without difficulty into his stomach.

From that time cases were frequently reported, but little of importance was added to our knowledge of the subject till 1895, when Rosenheim (36) examined a case for the first time with an oesophagoscope, and 1897, when Rumpel first employed the X-rays for investigating the condition.

As is only natural, the etiological factors assigned to the early cases were vague and, in the light of modern knowledge, unsatisfactory. Both Purton and Rokitansky noted that in their cases the immediate cause appeared to be contusion of the chest. v. Luschka (21), describing a case in 1868, ascribed it to the severe catarrh of the oesophagus which was present ; this is now known to be a secondary effect. In the majority of instances, however, no cause was found, and the term idiopathic, that refuge of ignorance, was applied.

Handford (11), described a case of dilatation of the oesophagus accompanied by hypertrophy of the heart, and believed the dilatation to be secondary to compression of the oesophagus between the heart and the diaphragm. This connexion with hypertrophy of the heart was noted also by Pitt (28) and Rolleston (35), and a woman with achalasia of the cardia, shown by Hurst (14)

[1] Received June 3, 1930.

at the Clinical Section of the Royal Society of Medicine in 1915, had mitral stenosis and a very dilated left auricle.

Zenker and Ziemssen in 1877 and Morrell Mackenzie (22) suggested that the condition was due to 'diminished contractile power' or 'general weakness' of the oesophageal musculature, and this hypothesis has been accepted and expanded by several recent authors, notably Rosenheim. Whether such a paralysis could exist as a primary condition it is difficult to say; but it is certain that this is not the explanation of the majority of cases, if only because of the muscular hypertrophy which is always found and which indicates that the oesophagus must have made violent efforts to overcome some obstruction. It is to the failure of these efforts that the dilatation must be due. As no organic obstruction is ever found, the cardiac orifice being of normal size and admitting the passage of a finger without any difficulty, it is obvious that the obstruction must be functional.

All the earlier theories began to lose prominence in 1888, when, as a report of the physiological investigations of Kronecker and Meltzer (18) on deglutition and its nervous control, the suggestion of a nervous pathogenesis was first put forward to explain how obstruction could occur at the cardiac sphincter in the absence of obvious organic disease.

In 1888 Meltzer of New York and Mikulicz independently suggested that owing to a spasmodic contraction of the cardiac sphincter food was prevented from entering the stomach and, collecting in the oesophagus, produced the hypertrophy and dilatation characteristic of the established disease. This idea was at once widely accepted in Germany and shortly afterwards in England and America, in which country, in spite of its failure to account adequately for all of the facts, it has remained the most popular hypothesis up to the present time.

During the same year Einhorn (7) gave a clinical description of a case in which dilatation was marked, though no obstruction was felt on passing a tube into the stomach. He came to the conclusion that he was dealing with 'a lack in the reflex relaxation or opening of the cardia during the act of swallowing'. He points out that Kronecker and Meltzer have shown that 'every act of swallowing easily opens the cardia by reflex action'. He then suggests that if 'the centre or the circuit of this reflex action is in any way disturbed, so that the cardia does not relax when swallowing, there will necessarily result a slight difficulty in transferring the food from the oesophagus into the stomach'. This is apparently the first suggestion that absence of relaxation, or achalasia, was the condition primarily concerned in the production of the disease. Little or no notice was taken of it, however, and no mention of this hypothesis is found again in the literature until 1896, when Rolleston (35), knowing nothing of Einhorn's paper, arrived at a similar conclusion himself in discussing an autopsy specimen of oesophagectasia. Again the hypothesis escaped notice and the belief in cardiospasm held the field until 1913, when Hurst (14), oblivious of his two predecessors, made the suggestion a third time that the condition was one of non-

relaxation of the sphincter rather than spasm, and in 1915 introduced, on Sir Cooper Perry's suggestion, the term 'achalasia' of the cardia (a, absence of; χάλασις, relaxation) for the disease.

While these last two hypotheses have attracted most attention during the last fourteen years, attempts have been made to explain the obstruction of the cardia as due, in part at least, to the mechanical effect of structures lying outside, or to abnormal anatomical relations of the lower part of the oesophagus. Hill (13) and Jackson (16) both suggested that the fault lies in the muscle-bundles of the diaphragm which encircle the oesophagus at the hiatus, the former believing that there is an absence of the normal relaxation of the diaphragm on swallowing, and the latter that there is an actual spasm of its fibres—a phrenospasm. Many arguments may be adduced against such conjectures, amongst which is the fact that, as will be pointed out below, the dilatation of the oesophagus often extends through the diaphragm into the abdomen. Mosher (27) has described two anatomical changes in the intra-abdominal portion which he believes to play a part in the etiology of the disease, namely the 'liver tunnel' or deep oesophageal groove in the liver, and the backward bend at the cardiac orifice which, only slight when present in normal degree, may, he believes, be accentuated greatly in case of oesophagectasia. Although the question of the liver-tunnel has not been carefully examined, it is difficult to believe that the groove can ever attain such a depth as to produce the degree of obstruction which is obviously present. As to the second of these suggestions, there is certainly a kinking of the lower end to be noted in the dilated oesophagus after its passage through the diaphragm, but this would seem to be a direct result of the dilatation rather than the cause of the disease.

The Anatomy of the Cardiac Sphincter and the Physiology of Deglutition.

In order to understand the mechanism by which the failure of the cardia to open and the subsequent hypertrophy and dilatation are brought about, it is necessary to consider the anatomy and nervous control of the lower end of the oesophagus and the events which occur during deglutition. From a radiological study of the act of swallowing in normal people and in patients suffering from achalasia of the cardia, we have come definitely to the conclusion that the last inch or more of the oesophagus has such a totally different function from that of the rest that it deserves to be regarded as a functional sphincter, whether an anatomical sphincter—a true condensation of circular muscle separating the oesophagus from the stomach—exists or not. When swallowing is not taking place, the postural tone of the circular muscle fibres of the cardiac sphincter is such that it has no potential lumen, in contrast with the cervical and thoracic oesophagus, which have a potential lumen at least an inch in diameter, although when empty their walls collapse and so completely obliterate it. Consequently the sphincter offers a definite resistance to the passage of food, whereas the rest of the oesophagus offers no resistance at all.

A true anatomical sphincter was described by Mathew Baillie (1) in 1807. Its existence has since then frequently been denied. It can, however, be readily demonstrated in still-born infants, in whom the relatively long cardiac sphincter is clearly differentiated from the rest of the oesophagus by the greater thickness of its muscular coat and by the pallor and prominent longitudinal rugae of its mucous membrane (Fig. 1). Poulton and Payne found on cutting longitudinally through the cardia into the oesophagus in adults that the lower two or three inches can often be seen to have a thicker muscular coat than the part immediately above, an observation which we have frequently been able to confirm. The absence of more obvious thickening of the circular muscular coat of the
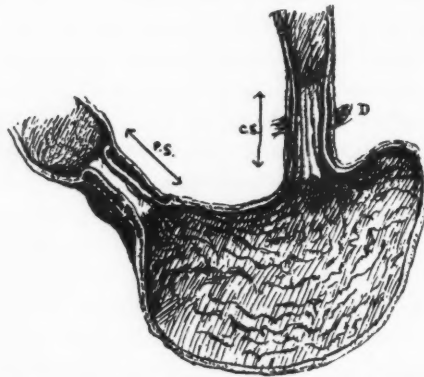

FIG. 1. Drawing of section through the stomach of a still-born infant. CS, cardiac sphincter with deep, pale, longitudinal rugae and thickened circular muscle. D, diaphragm embracing centre of sphincter. PL, pyloric sphincter.

cardiac sphincter compared with that of the pyloric, ileo-caecal, and anal sphincters, is probably due to the fact that the function of the cardiac sphincter differs from that of the others in being concerned in the prevention of regurgitation of gas and fluid from the stomach into the mouth, and only to a very minor extent in the regulation of the onward passage of the contents of the oesophagus. It is consequently never called upon to resist a degree of pressure anything approaching that which the other sphincters are able to withstand. The length of the sphincter corresponds roughly with that of the intra-abdominal oesophagus, but it often extends slightly above the diaphragm or begins a short distance below it.

The nerve supply to the oesophagus has long been a matter of controversy, and even at the present time it can hardly be said that the details have been settled with certainty. Gaskell (10) stated categorically that the oesophagus received no sympathetic supply; other writers, on the contrary, have stated that it receives sympathetic fibres throughout its whole course. The truth lies between the two extremes. The two great splanchnic (sympathetic) nerves supplying the stomach send branches with the inferior phrenic arteries up through the diaphragm to supply the lower part of the oesophagus. The exact extent of this sympathetic supply has never been accurately determined, but it seems probable that at least the whole of the sphincter receives a dual nerve supply. The vagus nerve sup-

plies the whole of the oesophagus, forming a ramifying plexus, *plexus gulae*, on the anterior and posterior surfaces, from which the fibres pass to the myenteric or Auerbach's plexus lying between the two muscle layers (Fig. 2). This plexus is composed of ganglion cells, which are to be looked upon as definite nerve relay stations and as a mechanism through which the isolated myenteric reflex can occur.

Dogiel (5) has shown that two types of ganglion cells exist in Auerbach's plexus, and states that the vagus fibres terminate around one of these—type II, while sympathetic fibres relay by means of type I. Gaskell, however, came to the conclusion that there is nothing to point to the sympathetic fibres ever
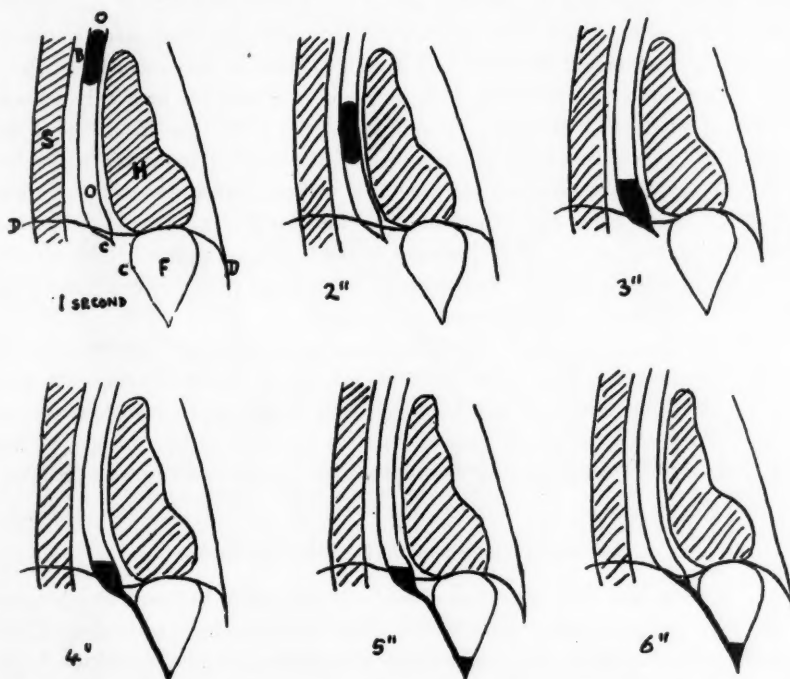

FIG. 3. Diagrams of the passage of a bolus of barium-containing food (B) through the oesophagus (O-O), as seen with the X-rays in successive seconds after swallowing. s, spine; H, heart; DD, diaphragm; CC, cardiac sphincter; F, fundus of stomach.

terminating in the plexus. While vagus fibres have definitely been shown to terminate around type II, such a relationship of sympathetic fibres to type I has never been demonstrated; indeed, as yet no fibres have definitely been traced to these cells. Further, Gaskell pointed out that, were it true that the sympathetic motor fibres were relayed through these ganglion cells, we should have here an example of pre-ganglionic fibre that was non-medullated, a condition otherwise unknown. To these arguments may be added the following: at least in the upper part of the oesophagus it is certain that the ganglion cells are all vagal, since no sympathetic fibres are supplied to this part of the alimentary canal. Moreover, in addition to being non-medullated, the sympathetic nerves

have already been once relayed in the extraspinal ganglia. The evidence, both direct and indirect, therefore, seems to eliminate the presence of ganglion cells of the sympathetic system in Auerbach's plexus.

In the process of deglutition food is thrust through the pharynx by the action of the tongue; the sphincter formed by the crico-pharyngeus muscle, which closes the upper end of the oesophagus at rest, relaxes and permits the food to enter the oesophagus, down which it is propelled by a peristaltic wave. The process was first observed with the X-rays by Hurst and his assistants (15) in 1907. The opaque food is seen to pass rapidly down the oesophagus to the cardia, where there is a momentary pause, the lower extremity of the shadow tapering to a point which corresponds with the upper end of the cardiac sphincter (Fig. 3). A moment later the food is seen to pass on into the stomach, and, where the shadow ended before as a point, it now extends in a thin stream, uniform in diameter and about an inch in length, to the cardiac orifice of the stomach, the stream representing the lumen of the cardiac sphincter, which has undergone active relaxation on the arrival of the peristaltic wave at the lower end of the oesophagus, in accordance with the Bayliss and Starling's 'law of peristalsis', according to which a wave of contraction is preceded by a wave of relaxation when peristalsis passes down a muscular tube. Directly the food enters the stomach the sphincter once more closes.

The involuntary part of deglutition may be regarded as merely a part of the myenteric reflex. This reflex, initiated voluntarily in the pharynx, can continue to act in the absence of any impulses from the central nervous system, and will in fact function after all connexion with the central nervous system has been severed until secondary degeneration of the isolated nerve plexus occurs.

Nervous Disorders of the Cardiac Sphincter.

It is clear that four abnormal conditions may affect the cardiac sphincter. While over-action of the vagus would produce a patulous condition of the sphincter with increased tone in the oesophagus above, destruction of the vagus in any part of its course would produce a failure of inhibition of the sphincter, which, without being in a condition of spasm, would remain closed in front of the bolus of food by reason of an achalasia or absence of relaxation. On the other hand, sympathetic stimulation would produce a true spasm of the sphincter, while destruction of the sympathetic fibres would allow the vagus unimpeded action. Of these results the second and the fourth must be produced by definite organic lesions; it is possible, however, that increased tonus of either the vagus or the sympathetic would be more frequently produced by a nervous reflex from some organic lesion in the abdomen, or, as Thriedling (37) has suggested, by means of an endocrine disturbance. It is the second and third of the above possibilities which have the greatest bearing on the pathology of oesophagectasia, namely, lack of vagus impulses, due to destruction of the nerve, producing achalasia of the cardia and over-action of the sympathetic producing cardio-spasm.

Kronecker and Meltzer (18) produced a condition of achalasia with secondary oesophageal hypertrophy and dilatation in rabbits by division of the vagus nerves in the neck. On the other hand, spasm of the sphincter may occur as a result of a short reflex in acute inflammation, peptic ulcer, and carcinoma of the lower end of the oesophagus, and possibly—though the evidence is inconclusive— as a result of a long reflex from a gastric or duodenal ulcer and the gall-bladder. It is very doubtful whether cardiospasm ever occurs as a purely functional disorder in so-called 'nervous' individuals, though it has been the custom to add this to the causes of dysphagia. So far as our experience goes, all cases of hyterical dysphagia are due to a disturbance in neuro-muscular control of the voluntary part of the act of deglutition; they involve the upper sphincter of the oesophagus and never the cardiac sphincter.
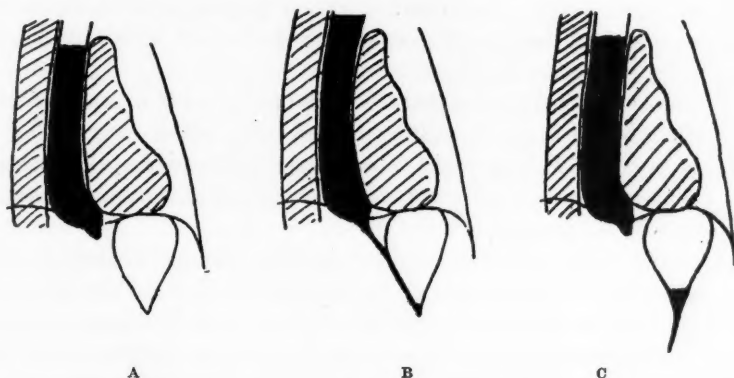

A   B   C

FIG. 4. Diagrams of oesophagus in achalasia of the cardia. A shows column of barium-containing food, 8 in. high, above closed cardia. B, after additional quantity of food swallowed, so that the taller column, being heavier, opens cardia and allows surplus to enter stomach. C, return to condition of (A) after surplus food over the 8 in. column has entered stomach.

Achalasia of the Cardiac Sphincter.

In achalasia of the cardia the column of food in the lower end of the oesophagus is seen with the X-rays to end in a blunt point at the upper extremity of the sphincter (Fig. 4 A). The distension of the oesophagus produced by stagnating food leads to powerful peristaltic waves which are not only excessively violent, as is easily seen with the X-rays, but continue at intervals throughout the day instead of occurring only in single waves as each mouthful is swallowed. This is the cause of the hypertrophy.

The powerful peristaltic waves are unable to overcome the obstruction offered by the closed cardia, because the dilatation of the oesophagus is so great that they are insufficiently deep to obliterate its lumen; they cannot therefore appreciably increase the pressure exerted on the cardia, their only effect being to churn the oesophageal contents. The resistance of the unrelaxed cardiac sphincter can be overcome by a pressure of about eight inches of water. Consequently, when a meal is taken no food passes into the stomach until the

contents of the oesophagus form a column about eight inches high (Fig. 4 B). Then, whenever anything is eaten or drunk, the cardia opens and allows food to pass till the height is again eight inches, when it closes once more.

In 1913 Hurst showed that the weight of a rubber tube filled with mercury was sufficient to cause it to drop without the slightest difficulty through the cardia into the stomach, the actual passage through the cardia being often inappreciable to the hand which holds the mercury bougie. With the aid of the X-rays we have several times watched it pass directly into the stomach, as if it met with no resistance at all. This would be quite impossible if the obstruction was due to spasm: the resistance offered to the introduction of the finger, for example, when the anal sphincter is in a condition of spasm is very considerable, and considerable force is required to overcome it. Moreover, the tube can be withdrawn with equal ease: it is not gripped, as it would be were a spasm present and as the finger is gripped when it is withdrawn from a spasmodically contracted anal sphincter.

We have occasionally found that the mercury tube meets with some obstruction when introduced and is tightly gripped when withdrawn, spasm being obviously present. This, however, always rapidly disappears with treatment of the oesophagitis, which had apparently led to the achalasia being temporarily complicated by the presence of reflex spasm.

Achalasia of the cardia may begin at any age. Langmead (19) observed a case in a female child, 16 months old, who started to retch and regurgitate soon after birth. The diagnosis was established by means of the X-rays and oesophagoscope. He also described the case of a girl of 13, whose symptoms dated from or near birth and disappeared with treatment by suggestion. He refers to a case of Ryle's in which suggestion had a similar satisfactory result, which he regards as evidence that the condition is of 'nervous origin'. But the remarkable fact about Ryle's case, which he omits to mention, is that although the symptoms disappeared after treatment by a faith-healer, the X-rays showed that the obstruction at the cardia was no less severe than before, the only result of suggestion being that the patient was induced to disregard his symptoms. Parkes Weber (40) collected the records of eleven other cases occurring in the first seven years of life, the youngest being one of Chevalier Jackson (16) in an infant two days old.

In a series of 23 cases seen by one of us, 12 were in men and 11 in women. The age of onset varied between 22 and 71, and in seven it was before the end of the thirtieth year.

Pathogenesis.

As has been pointed out in discussing the physiology of the cardiac sphincter, its permanent closure would occur if the vagus nerve in some part of its course were damaged or destroyed. Sympathetic stimulation leads to a spasm of the sphincter; but although such spasm does occur, usually as a result

of reflex action, through its very nature it must be intermittent rather than permanent, and it is very improbable that this temporary disability could ever produce a condition of oesophagectasia similar to that seen in achalasia. Kraus recognized clearly that the majority of cases of hypertrophy and dilatation of the oesophagus depended upon some lesion of the vagus, insisting that in every case the integrity of the nerve throughout its whole extent should be investigated. He himself describes a case in which the nerve fibres were degenerated, and in another Pollitzer (29) found the vagi buried in a mass of enlarged glands. Despite this, however, little attention was paid to the nervous system in these cases, and all histological investigations were focussed on the muscle coats of the oesophagus, which were considered by many to be the primary seat of the disease.

The state of preservation of Auerbach's plexus was wellnigh neglected; indeed, in only one or two cases in the whole literature is the plexus mentioned, and then only to be dismissed as not abnormal for reasons which will be discussed below. Attention, however, had been called to the part it must in all probability play in the causation of the disease, and Hurst in 1924 suggested that 'the majority of cases ... are caused by progressive organic disease involving Auerbach's plexus', although at that time no such lesion had been described.

In December, 1925, a patient, R. C., aged 67, was admitted to Guy's Hospital suffering from a carcinoma of the tongue. He was operated upon, but died two days later. At autopsy an hypertrophy of the circular muscle coat of the oesophagus was found, commencing opposite the bifurcation of the trachea and extending downwards for 9 cm. to end 4 cm. from the entrance to the stomach : there was no dilatation of the oesophageal lumen. This case was recognized by Rake (31) as probably representing an early stage of achalasia of the cardia before the compensatory hypertrophy had failed and dilatation had appeared. Similar cases had been described by Pitt (28), Rolleston (35), Ellieson (8), and Ehlers (6). Rolleston, in the discussion of his case, also concluded that it might represent a well-compensated case of achalasia of the cardia. If this were true, an excellent opportunity was offered to examine the condition of Auerbach's plexus.

Lesions of a subacute inflammatory nature involving the plexus were found by Rake (Fig. 5). The ganglia were increased in size and showed marked cell infiltration, lymphocytes being in predominance together with a few eosinophil and mast cells. The ganglion cells appeared to be degenerating and in places apparently were undergoing phagocytosis. The vessels surrounding the ganglia were dilated and surrounded by wandering cells. In the later stages there was disappearance of the ganglion cells and commencing fibrosis of the plexus. These changes, as had been expected, seeing the condition that resulted, were most marked at the cardia below the area of hypertrophy and became less obvious when traced up the oesophagus.

Since the examination of this case it has been possible to investigate the

condition of the plexus in two similar cases from the autopsy material of the London Hospital through the kindness of Professor Turnbull. Both showed changes identical with those described.

A few months later detailed examination was made by Rake of a series of cases of fully developed achalasia of the cardia with well-marked dilatation. It was found that, although the majority showed the final stage of the process—the non-committal scar—some of the intermediate steps could occasionally be observed. The inflammatory process around the plexus had subsided leaving perhaps a small collection of lymphocytes. The plexus showed gradual replacement by means of scar tissue (Fig. 6). The fact of greatest importance was the disappearance of all ganglion cells: not a single one could be found in the examination of 250 serial sections. In the final stage the plexus itself and the surrounding tissue were converted into a dense fibrous scar with dilated thin-walled blood-vessels; nothing of the original structure of the plexus could be seen (Fig. 7). It is apparently this complete destruction and replacement of the ganglia which led to the lesion being overlooked for so long: the small fibrous scar is easily mistaken for the connective tissue normally present between the muscle coats by an observer who is not particularly interested in the plexus.

With the demonstration of this inflammatory and destructive lesion of Auerbach's plexus the conditions laid down as necessary for the production of achalasia are fulfilled. In every one of the eleven cases, three of compensating hypertrophy and eight of the established disease, which have been examined up to the present this lesion has been found. The factor or factors concerned in its production are unknown. It has been suggested that the inflammation spreads to the plexus from the lumen of the oesophagus, for example, from an oesophagitis. As against this it may be said that in the early cases no oesophagitis is present, although the plexus shows acute inflammation. Moreover, it is believed that the oesophagitis is always secondary to the achalasia, which in itself is produced by the inflammation of the plexus. Syphilis as an etiological factor was discussed in the first case described by Rake, and one of Hurst's early cases had signs of tabes, but the blood gave a negative Wassermann reaction. This is perhaps worthy of consideration, but the tendency to fall back upon syphilis in the case of any etiological uncertainty must be remembered. Dr. C. P. Symonds has suggested to us that the condition might sometimes be due to an infective ganglionitis analogous to the inflammation of the posterior root ganglia in herpes zoster. Primary vascular disease, congenital abiotrophy, and other suggestions have been put forward tentatively whenever the condition has been discussed, but for the moment the fact remains that nothing is known as to how this inflammatory process is caused.

It must be emphasized that, although this definite lesion has been found in all the cases yet examined by Rake, and has since been found by Cameron (3) in eight cases and by Mosher and McGregor (27) in one, it cannot be asserted that it is the only lesion capable of producing the disease. While all the evidence accumulated at the moment would suggest that it is the cause in the majority of

cases, extensive bilateral involvement and destruction of both the vagi in any part of their course would give rise to an achalasia clinically indistinguishable from that under consideration. Possibly peripheral neuritis accounted for a case described by Rolleston and another by Looser (20) in which the condition developed after whooping cough and diphtheria respectively.

The Morbid Anatomy.

As has been indicated already, achalasia of the cardia in the early stages produces marked hypertrophy of the muscular wall, particularly of the circular muscle, above the region of non-relaxation. This hypertrophy continues to increase so long as it still proves sufficient to compensate for and overcome the obstruction, and during this time no symptoms will appear. It is for this reason that these cases are not recognized during life, but are discovered accidentally *post mortem*. Owing to the permanent nature of the obstruction at the cardia the hypertrophy in time fails to suffice, food accumulates in the oesophagus, and secondary dilatation appears. With the progress of the lesion there is a further steady increase in size, and in this way is produced the greatly dilated oesophagus that is so striking a feature of long-standing cases. Nevertheless even in these examples, as has already been mentioned, hypertrophy of the circular muscle layer may still be seen, a fact that was missed by many of the earlier observers.

The degree of dilatation present in advanced cases has often been a matter for comment. Such marked dilatation is never seen in the oesophagus following organic strictures even of long duration, and is comparable only with the dilatation of the colon in Hirschsprung's disease or of the ureters in so-called idiopathic dilatation of the ureters or megalo-ureter. It is probable that both these diseases have a pathology similar to that described above. This was first suggested by Hurst in connexion with Hirschsprung's disease in 1919, and megalo-ureter in 1930, and such changes have recently been observed in the former by J. A. M. Cameron (3) and by Professor Rhea of Montreal. A consideration of some of the facts already discussed suggests the probable reason for this degree of dilatation. The normal tone of the oesophagus is maintained by the vagus : with the vagi cut Langley found a marked fall in tone accompanied by more ready dilatation. The gradual destruction of Auerbach's plexus by a slowly progressive lesion would produce a concomitant loss of tone which may well account for the extreme degree of dilatation.

The increase in size of the oesophagus always ends some distance from the cardiac orifice, but the actual point of termination varies according to the varying length of the cardiac sphincter. In most cases the dilatation ends at about the level of the diaphragm. This is one of the facts that has led to the assumption that the cause of the condition lies in some faulty contraction or absence of relaxation of the diaphragm. However, against this is the fact that the dilatation occasionally ends just above the diaphragm and more frequently extends through the diaphragm to end within the abdomen (Barlow).

In such cases we have recognized with the X-rays a definite constriction in the dilated lower end of the oesophagus at the point where it passes through the diaphragm ; this is due to the resistance to distension offered by the fibrous tissue of the oesophageal aperture of the diaphragm.

The lumen of the cardiac sphincter is potential rather than actual, and the thickness of its wall is never greater than normal ; hypertrophy of the circular fibres, such as might reasonably be expected to follow upon a constant spasm of the sphincter if this had existed, is never found. The absence of hypertrophy of the sphincter was very clearly seen during life in one patient on whom Mr. R. P. Rowlands performed a Rammstedt's operation on the sphincter, and the same observation was made by Sir Charles Gordon Watson in three and by Rieder in six cases in which they performed this operation. In each case the sphincter was constituted by the whole of the intra-abdominal oesophagus. As its division gave complete relief in Rowland's case, the diaphragm being untouched, it is obvious that the diaphragm itself could have taken no part in causing the obstruction.

Whereas the increase in width of the oesophagus is constant and extreme, an increase in length is not so usual. When present it forces the oesophagus to take a tortuous course through the chest. Owing to the fact that the heart lies in the main on the left side, the lengthened oesophagus in its lower part forms a curve convex to the right and the dependent part of this curve rests like a sac on the top of the diaphragm. The solid food, instead of passing gradually down to the cardia, now sinks rapidly through the column of stagnating and decomposing fluid mixture of food and saliva to enter this sac, which is thereby increased in size and in time acts as an additional obstruction at the cardia by reason of the valve-like action of its lateral traction.

The stagnation of food and saliva within the oesophagus is often extreme, amounting usually to many hundred cubic centimetres. This mixture becomes readily infected, and the irritating products of fermentation and putrefaction give rise to oesophagitis, which is always present in chronic cases. It may be accompanied by ulceration of the mucosa, usually superficial but in some cases extending so deeply as to perforate into the pleural cavity.

The shallow ulcers may finally heal and lead in turn to epithelial hyperplasia with the production of leucoplakia and small wart-like nodules, which are mentioned frequently in the literature (e. g. Kraus (17)). As a final stage of this change a squamous-celled carcinoma may arise. The occurrence of carcinoma commencing within a dilated oesophagus in a man of 84, who had had difficulty in swallowing for over forty years, was described and illustrated by Hilton Fagge (9) in 1872. Other similar cases have been described by others, and in 1926 we observed one in a man of 69, who had had symptoms of achalasia of cardia for thirty-five years. No attempt, however, has been made in the past to connect the carcinoma with the foci of hyperplasia found in other specimens. In a case seen recently a man of 43 was admitted to the hospital in the last stages of malignant cachexia. He gave a history of some disability in swallowing for

many years, but his whole story was very vague. Secondary nodules of carcinoma were felt in the right tibia and elsewhere, but the primary tumour was not found before death, which occurred within four days. At autopsy a greatly dilated oesophagus was found with the dilatation ending some 2 cm. from the stomach. The cardiac sphincter showed no hypertrophy. It was a characteristic case of achalasia. On opening the oesophagus it was found to contain quantities of decomposing, fluid food debris. The mucous membrane was severely inflamed and had many epithelial warts scattered over its surface. One of these had become malignant. The association of carcinoma with epithelial over-growth in the oesophagus is of interest in connexion with its occurrence in the stomach and colon.

In 1925 Hurst described a case he had seen in 1917 of a man of 33 with typical symptoms of achalasia of the cardia, in which the X-rays showed that the dilated oesophagus was associated with a large diverticulum two inches above the cardia. The patient was completely relieved by means of a mercury tube. Four similar cases have been recorded: in one the dilated oesophagus and pouch were discovered *post mortem* (Kraus), the remaining three being diagnosed with the X-rays (Vinson (39), Dessecker (4)).

The connexion of a dilated stomach with cardiac achalasia has occasionally been observed. In the majority of museum specimens kept with the stomach complete the large size of the organ is noticeable. While it is fully realized that the size of the stomach at autopsy is a very variable factor, yet it would seem that this dilatation is too marked to be ignored. It is, however, rare, as although a similar appearance was noted on X-ray examination by Hill (13), the stomach was normal in size in all the cases we have examined radiologically. It would seem probable that the dilatation of the stomach might be produced by destruction of Auerbach's plexus in the pyloric region, but in spite of careful search by Rake no lesions of the plexus have yet been observed.

Finally, an associated finding which is almost constant is hypertrophy of the salivary glands, especially of the submaxillary glands. This may be observed clinically. At autopsy the glands present a normal appearance save for the increase in size; on microscopical examination nothing is seen except an increase in the size and number of the alveoli. The hypertrophy is probably due to prolonged over-activity of the glands. Thus excessive salivation is a very common symptom in oesophageal obstruction, whatever the cause, and it is sometimes a cause of much distress to the patient. The dilated oesophagus always contains a great deal of saliva as well as food. Roger (33) in 1907 showed experimentally that mechanical irritation of the oesophagus caused reflex salivation, and it seems likely that the salivation associated with oesophageal obstruction is due to reflex irritation of the mucosa by decomposing food.

Symptoms.

The symptoms were fully described by Hurst in 1915 in this Journal and will therefore only be briefly summarized here. An individual, who has

previously never suffered from indigestion, one day feels that his food is 'sticking' deeply beneath the lower end of his sternum. After a time the discomfort, which rarely amounts to pain, passes away, either spontaneously or after ejection of the food—ejection, not vomiting, as the stomach takes no part in the action, which is unaccompanied by nausea. The food is undigested and alkaline, unless it has been retained sufficiently long to undergo fermentation, and it is mixed with abundant mucous saliva. The ejection is generally a more or less voluntary action, which the patient often learns to perform whenever the substernal sensation becomes sufficiently unpleasant. Regurgitation rarely occurs on lying down, although the oesophagus is always filled with a large quantity of food and mucus, because the upper extremity is kept closed by the sphincter action of the crico-pharyngeus muscle. The first attack may be followed by similar attacks after every subsequent meal, or there may at first be intervals of varying length, but eventually all intermissions cease. The patient learns to eat very slowly and to choose food of fluid and semi-fluid consistence. He slowly loses weight, but finally equilibrium is established, and he is often able to carry on his occupation, though with his strength and energy greatly impaired.

Though the symptoms are very often mistaken for gastritis or some other disorder of the stomach, a carefully elicited history and the examination of the ejected material should exclude such a diagnosis. The only conditions giving rise to somewhat similar symptoms are cancer of the lower end of the oesophagus and cancer of the fundus of the stomach. In these, however, the onset is much more insidious, and the dysphagia gets progressively worse without intermission till complete obstruction occurs after a comparatively short time, except in old people, in whom the disease may advance extremely slowly. In achalasia, on the other hand, the obstruction is no greater at the end of ten years than it was at the onset, which is always quite sudden. In cancer loss of weight and strength are generally more rapid, and the condition rarely occurs before the age of 45 or 50, whereas achalasia may occur at any age.

The X-rays at once settle the diagnosis; the oesophagus is found to be greatly dilated, and if it is previously emptied by a tube or by the voluntary ejection of its contents, the whole of the opaque meal is seen to accumulate in the oesophagus. In spite of violent, but intermittent, peristalsis, nothing passes through the cardiac sphincter till the food forms a column about 8 in. in height, when a fine straight line, representing the lumen of the sphincter, is seen passing from about the level of the diaphragm to the stomach. In cancer the oesophagus is never greatly dilated and the whole of the opaque meal gradually passes into the stomach unless it is ejected, so that no large accumulation occurs. The lumen of the affected part is irregular in width and direction instead of being straight and uniform in diameter. Occult blood is found constantly in the stools in cancer, but never in uncomplicated achalasia.

Oesophagoscopy is superfluous, as the diagnosis can be made with more certainty and much less unpleasantness by means of the X-rays. The passage

of an ordinary bougie is dangerous as well as useless, as the lower end of the oesophagus is so dilated that it forms a blind ending, from the left side of which the lumen of the cardiac sphincter passes; consequently a bougie generally misses the sphincter, and, unless great care is taken, it may damage the oesophageal wall. A flexible rubber tube filled with mercury, sufficiently heavy to find its own way without being pushed, passes through the closed sphincter without any appreciable resistance being felt. A growth, on the other hand, always forms an insuperable obstruction to the passage of the mercury bougie.

Treatment.

Dilatation of the sphincter. As it is presumably impossible to restore the power of relaxation to the closed cardiac sphincter, the object of treatment must be to dilate it to such an extent that it no longer offers any resistance to the passage of food into the stomach. This can be done most easily and with least discomfort and danger by means of the mercury bougies which were first described by Hurst in 1913. Rubber tubes varying in diameter between 33/64 and 46/64 inch (gauge Nos. 28 to 34), 31 inches long, and each containing the same weight of mercury (1 lb. 5 oz.) which has been found by experience to be sufficient to force the closed sphincter, are now obtainable. It is best to pass the bougies on the first occasion during an X-ray examination; it is then seen that they pass without deflection straight into the stomach. A mark should be made on the bougie at the level of the teeth when its two lower inches are within the stomach. Successively larger tubes are passed at a single sitting, and in most cases the largest one meets with as little resistance as the smallest. The patient is then taught to pass the largest bougie on himself before each meal. He finds at once that a meal taken after its passage enters his stomach without difficulty. For a few days the bougie should be retained in position on each occasion for as nearly five minutes as possible; then the time is reduced before lunch and dinner, and often within a week the midday passage can be given up entirely. Later the bougie is passed in the morning only, and the time it is kept down is steadily reduced. After a time in favourable cases the bougie is only passed on alternate days, then once a week, and finally its use is discontinued, but it is kept by the patient so that he can pass it if at any time he feels that some slight obstruction has returned.

Until 1925 the largest bougie we employed was No. 24. With No. 32, which, in spite of its alarming appearance, causes no more discomfort than the smaller one, improvement is much more rapid. But even with No. 24 sufficient improvement occurred in the majority of cases for patients to be able to discontinue its use after an interval of varying duration; in one patient, who was fortunate enough to have his condition diagnosed correctly on the actual day of the onset of symptoms, the passage of the bougie on a single occasion produced a complete and permanent cure. Another man was able to go through the

hardships of four and a half years of active service in the war without any recurrence. Occasionally patients have found it necessary to continue to pass the bougie once or twice a day, but as they quickly get accustomed to it this is no great hardship. With the larger tube now in use this is very rarely necessary.

Another method of dilating the closed sphincter has been very widely employed. It was first devised by Russell in 1898 and was greatly improved by Plummer ten years later. The patient slowly swallows three yards of silk thread in the afternoon and another three yards the following morning; sufficient reaches the intestine to prevent its withdrawal when it is pulled tight. The instrument is threaded over the silk, at the lower end of which there is a bag which can in this way be introduced into the sphincter. The bag is then forcibly dilated by hydrostatic pressure. The treatment is very painful and has on several occasions led to death by splitting of the sphincter. When carefully used, however, the danger is small. It has, however, no advantage over the mercury tube, and it proved unsuccessful in the only one of our cases in which no lasting improvement followed the use of the mercury tube, which the patient had used every day for three or four years.

Treatment of the oesophagitis. The excessive secretion of mucus resulting from the oesophagitis, which is always present in chronic cases, leads to the retention of particles of food between the swollen rugae of the mucous membrane. It is therefore necessary to give the patient a diet containing no pips, skins, or vegetable fragments, which would be likely to act as irritants. He should chew his food thoroughly, eat slowly, and finish each meal by drinking half a pint of water or milk in order to wash the last traces of food into his stomach. During the first week of treatment it is advisable to give nothing but four feeds a day, each consisting of one pint of milk, which may contain glucose or a beaten-up egg; this is generally quite sufficient to cause a gain in weight of 2 or 3 lb. in an emaciated patient. Many learn to eject the contents of their dilated oesophagus voluntarily. Any one who can do this should be encouraged to evacuate the oesophagus half an hour after each meal, and then drink half a pint of water and evacuate at once as much of it as possible. As a rule a small quantity of food and a good deal of mucus are still present during the first few days of treatment, but the quantity of each gradually gets less. When there is no longer any residue to evacuate and no water can be returned, the oesophagitis as well as the achalasia of the cardia can be considered to be cured. In very long-standing cases with severe oesophagitis, if the patient is unable to evacuate his oesophagus voluntarily, it should be emptied and washed out with a rubber tube attached to a Senoran's evacuator half an hour after each meal, until all signs of oesophagitis and oesophageal retention have disappeared.

Surgery. In the very rare cases in which treatment with a mercury tube gives insufficient relief, an operation becomes necessary. The one most commonly performed is digital dilatation through the opened stomach. This was first practised by Mikulicz in 1882, but as death occurred in some of his cases

owing to rupture of the oesophagus, the operation never became popu ar. Recently, however, it has been warmly advocated by Walton, who has h d excellent results in thirteen out of his fourteen cases; the remaining case, a ma of 66, died of heart failure. In 1928 we saw a patient who had had the opera tion performed in 1926. She was relieved for about a fortnight, when the symptoms returned in an aggravated form. She could only swallow fluids, and in the next year lost a stone in weight. She complained of a feeling of con striction in the region of the cardia, which frequently developed to attacks of very severe pain lasting three or four minutes. We found that the achalasia had become complicated by a fibrous stricture, so that instead of the usual tapering termination of the oesophagus seen with the X-rays there was a very irregular line, which would have suggested the presence of a growth if the history had not been known. Dilatation was successfully carried out by means of mercury bougies, but instead of being quite painless the passage on each occasion caused a considerable amount of pain, which lasted for an hour or more. The result of treatment was satisfactory, as the patient was finally able to eat ordinary food without difficulty. It was thought necessary, however, that she should continue to pass the largest tube herself every day in order to prevent contraction of the fibrous tissue taking place again. When X-rayed some months later, it was found that a continuous stream now passed through the oesophagus into the stomach, and that although emptying of the oesophagus was slow no accumulation took place within it.

Exner in 1917 performed an anastomosis between the abdominal oesophagus and the stomach, and more recently Grey Turner (38) has performed this opera tion on two of his patients, but the operation is extremely difficult and no more likely to be successful than stretching the sphincter. Heller in 1914 made a longitudinal incision through the muscular wall of the abdominal oesophagus, the operation being analogous with Rammstedt's operation for congenital pyloric stenosis. He collected sixteen cases in which the operation was performed with good results in twelve and no mortality. In one of our cases Mr. R. P. Rowlands performed this operation and the patient was still completely well when last seen four years later.

Rieder (32), thinking that the condition was due to cardiospasm, divided both vagi. The dysphagia was actually aggravated,—additional evidence that achalasia due to under-activity of the vagus rather than spasm due to its over activity is the cause.

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DESCRIPTION OF PLATE

PLATE 25, FIG. 2. Microphotograph of a normal ganglion of Auerbach's plexus in the lower end of the oesophagus. × 50.

FIG. 5. Microphotograph of ganglion of Auerbach's plexus in lower end of oesophagus, showing cell infiltration and degeneration of ganglion cells in achalasia of the cardia with muscular hypertrophy but no dilatation of oesophagus. × 50.

FIG. 6. Section through cardiac end of oesophagus in Mr. Grey Turner's case of achalasia, to show round-cell infiltration (R) and fibrosis (F) of Auerbach's plexus, with complete disappearance of ganglion cells, none being seen in any of 250 serial sections. × 50.

FIG. 7. Section through oesophageal wall in Mr. John Morley's case of achalasia of the cardia in a female of 39 with 16 years' history. It shows fibrous scar occupying the normal site of the plexus. × 65.
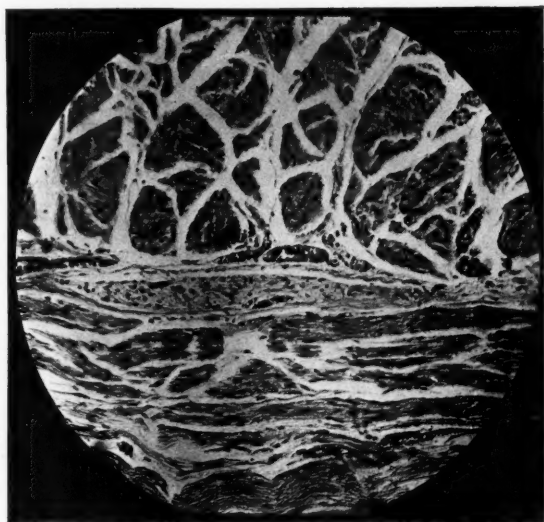
FIG. 2. Microphotograph of a normal ganglion of Auerbach's plexus in the lower end of the oesophagus. × 50.

FIG. 6. Section through cardiac end of oesophagus in Mr. Grey Turner's case of achalasia, to show round-cell infiltration (R) and fibrosis (F) of Auerbach's plexus, with complete disappearance of ganglion cells, none being seen in any of 250 serial sections.   × 50.
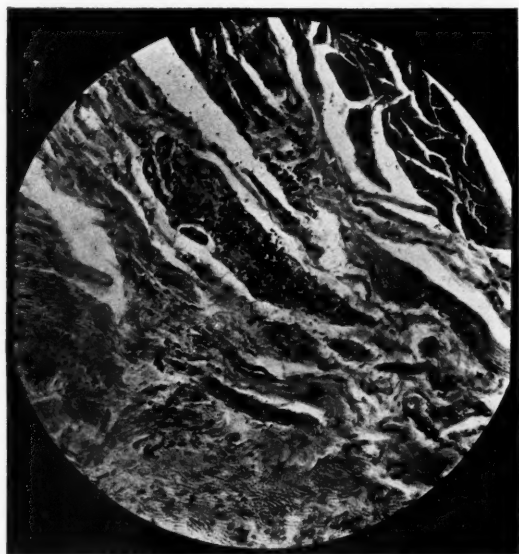

FIG. 5. Microphotograph of ganglion of Auerbach's plexus in lower end of oesophagus, showing cell infiltration and degeneration of ganglion cells in achalasia of the cardia with muscular hypertrophy but no dilatation of oesophagus.   × 50.

FIG. 7. Section through oesophageal wall in Mr. John Morley's case of achalasia of the cardia in a female of 39 with 16 years' history. It shows fibrous scar occupying the normal site of the plexus.   × 65.

PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

TWENTY-THIRD ANNUAL GENERAL MEETING

THE TWENTY-THIRD ANNUAL GENERAL MEETING was held at Cambridge on Friday and Saturday, April 5 and 6, 1929, in the Botany School. The proceedings began at 10 a.m.

The President, Professor J. Hill Abram, was in the Chair.

The Minutes of the last Annual Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Election of Officers.

President. Sir Humphry Rolleston was elected President for 1929–30. On his election he took the Chair and expressed the thanks of the Association to the retiring President for his services during the past year.

Honorary Member. Professor J. Hill Abram was elected an Honorary Member.

Election of Officers, members of the Executive Committee, and new members followed.

President. Sir Humphry Rolleston,

Treasurer. Dr. H. Morley Fletcher.

Secretary. Dr. H. Letheby Tidy.

Members for England :

Dr. W. Langdon Brown.
Dr. Carey Coombs.
Dr. Gordon M. Holmes.
Dr. J. W. McNee.
Dr. J. C. Matthews.
Professor A. Ramsbottom.

Members for Scotland :

Dr. A. Greig Anderson.
Dr. L. Findlay.
Dr. R. A. Fleming.

Members for Ireland :

Dr. S. B. Boyd Campbell.
Sir Thomas Houston.
Professor T. G. Moorhead.

ASSOCIATION OF PHYSICIANS

The following were elected Members:

William John ADIE, M.D., Assistant Physician, Charing Cross Hospital.

Hugh BARBER, M.D., Senior Physician, Derbyshire Royal Infirmary, Derby.

David Evan BEDFORD, M.D., Assistant Physician, Middlesex Hospital.

David CAMPBELL, M.D., Physician, Western Infirmary, Glasgow.

Hugh Hadfield CARLETON, M.D., Assistant Physician, General Hospital, Bristol.

Henry COHEN, M.D., Assistant Physician, Royal Infirmary, Liverpool.

John Forest SMITH, M.R.C.P., Assistant Physician, St. Thomas's Hospital.

Edward T. FREEMAN, M.D., Assistant Physician, Mater Misericordiae Hospital, Dublin.

Robert Dick GILLESPIE, M.D., Physician, Guy's Hospital.

Donald George HALL, M.D., Physician, Royal Sussex County Hospital, Brighton.

Alexander JOE, M.D., Medical Superintendent, North-Western Hospital, Hampstead.

William MacADAM, M.D., Assistant Physician, General Infirmary, Leeds.

Andrew RUTHERFORD, M.B., Assistant Physician, Royal Infirmary, Edinburgh.

John Andrew SMYTH, M.D., Assistant Physician, Royal Victoria Hospital, Belfast.

Presentation of Treasurer's Accounts. Dr. Morley Fletcher presented the Annual Accounts, which were adopted. They showed a balance of £230 4s. 9d.

Annual General Meeting in 1930. It was agreed that the Association should meet in London in 1930.

Extra-Ordinary Members. The following addition to the Rules was moved on behalf of the Executive Committee, and carried unanimously:

> 'Ordinary Members of not less than 15 years' standing, on ceasing to be qualified under Rule 2, shall be eligible to apply for election as Extra-Ordinary Members on nomination by the Executive Committee. Such Members shall have the rights and privileges of Ordinary Members except that of service as a representative on the Executive Committee, but shall not be subject to Rule 20. The number of such Members elected annually shall not exceed eight.'

Quarterly Journal of Medicine. (a) *Co-operation of the Association with the Board of Editors.* The meeting confirmed the following arrangements which had been made between the Executive Committee and the Board of Editors:

1. That the Treasurer should attend the meetings of the Board of Editors.

2. That a member of the Board of Editors should be co-opted on the Committee. Dr. R. Hutchison had consented to act as representative of the Board of Editors.

(b) *Appointment of New Editors.* Dr. Morley Fletcher, on behalf of the Executive Committee, recommended the appointment of Dr. A. G. Gibson and Dr. A. F. Hurst as Editors of the *Journal* on the nomination of the Board of Editors, in place of Sir Archibald Garrod and Sir William Hale-White, who had resigned.

The meeting passed a cordial vote of thanks to Sir William Hale-White for his long services on the Board of Editors.

SCIENTIFIC BUSINESS.

Friday Morning Session.

1. Dr. J. ALDREN WRIGHT on *Rat-bite Fever from a Kitten.* A woman was bitten on the hand by a kitten. The wound healed quickly, but two weeks after the bite it reopened, the axillary glands became swollen and tender, and from this time the patient suffered from periodical attacks consisting of pyrexia, painful glands and joints, vomiting and sweating. Each attack lasted about two days and recurred at intervals of five days. Three injections of N.A.B. (1·35 grammes in all) sufficed to cure the illness.

2. Dr. LEWIS SMITH communicated an example of *Nephritis following Rat-bite.* The case was that of a young woman presenting the usual signs and symptoms of chronic nephritis without cardio-vascular involvement, with a marked degree of renal inefficiency, and a high blood-urea. Twelve years before, a severe rat-bite had been followed by a serious illness with the classical symptoms of rat-bite fever. For the previous two years she had been losing strength. The Wassermann reaction of her blood was positive, but no history or evidence of syphilis in the patient, her husband, or children, was detected. A course of intravenous injections of N.A.B. was followed by marked improvement, and three years afterwards, her general health and renal efficiency were approximately normal, though the urine still showed a trace of albumin. It was suggested that the nephritis had resulted from infection with the *Spirillum minus.*

Dr. McNee mentioned a case of nephritis following rat-bite.

Sir William Willcox and others joined in the discussion.

3. Dr. J. F. GASKELL and Dr. C. H. WHITTLE (introduced) showed the results of experiments correlating a series of human pulmonary lesions due to the pneumococcus and experimental lesions in rabbits produced by the pneumococci isolated from these lesions. A fairly close agreement was claimed, and it is therefore justifiable to apply the experimental results obtained in the rabbit to the elucidation of the pathology of pneumococcal lesions in man, and to use the titre to the mouse as a convenient measure of the pathogenic power of a given pneumococcal strain.

Drs. Findlay and Coope discussed this communication.

4. Sir HUMPHRY ROLLESTON and Dr. E. W. DIXON on *The Experimental Production of High Blood-pressure.* The experiments included injections of kaolin, which clogged the Pacchionian bodies. This prevents the absorption of cerebro-spinal fluid, and results in a rise of cerebro-spinal pressure and of blood-pressure.

Drs. Gaskell, Parkes Weber, and Cohen took part in the discussion.

5. Sir THOMAS HOUSTON described *Two Cases illustrating the Clinical Significance of the 'Smooth and Rough' Forms of Enterococcus.* The smooth form of the enterococcus was isolated from both. The cases suggested that the enterococcus, when it becomes infective, changes to the smooth form, and this may again in the tissue revert to the rough form, owing to a partial immunity developed by an acute infection with the organism.

6. Dr. O. LEYTON on *The Administration of Insulin in Suspension.* Insulin suspended in castor oil was injected in cases of diabetes. Blood-sugar curves showed that the result was more lasting than by ordinary methods.

2–3 p.m.

Demonstrations were given by Drs. Dixon, Adrian, Györgyi, Barcroft, and others in the various laboratories.

ASSOCIATION OF PHYSICIANS

3 p.m. *Afternoon Session.*

1. Dr. F. PARKES WEBER made a communication on *Naevus anaemicus (Ischaemicus)*. In both his cases (a man aged 39 and a woman aged 32) the blotchy and grouped distribution of the lesion on the affected region was a striking feature. The contrast between the pale ischaemic areas and the surrounding skin could be heightened by rubbing or gentle stimulation. But on the application of very hot water the capillaries of the ischaemic areas could be made to dilate, and these areas then became as red as the surrounding skin. von Recklinghausen's disease had in at least two cases been known to be associated with naevus ischaemicus.

2. Dr. ADAM PATRICK made a communication on *A Case of Cyclical Pyrexia associated with a Tumour of the Thyroid*. The patient, a woman aged 30, showed cyclical pyrexia, slight in degree, each wave terminating with the onset of menstruation. This was apparently an exaggeration of the slight periodic variation in temperature which is known to occur in the healthy woman. In addition psychasthenic symptoms were present, and were so severe as to compel her to give up work. The tumour, an adenoma, was removed by operation, and three months later both pyrexia and psychasthenia had disappeared. The patient remained well.

3. Dr. THEODORE THOMPSON on *Paradoxical Embolism*. In a small proportion of cases of thrombosis in the systemic veins, embolism occurs not only in the lungs but also in the systemic arteries, most commonly in the cerebral, renal, and splenic arteries. The embolus passes from the right side of the heart to the left through a patent foramen ovale. The foramen ovale remains patent in about 33 per cent. of cases coming to necropsy, and is 0·7 cm. or larger in 6 per cent. of the cases. Among 50 cases of cerebral embolism, in 3 only paradoxical embolism was demonstrated, a venous thrombosis being present, a laminated ante-mortem clot found in the artery, and a patent foramen ovale existing. Details of six new cases were described. The paradoxical embolism in most cases occurred a few hours after a pulmonary embolism. It was shown that obstruction in the pulmonary artery or one of its branches markedly increased the pressure in the right auricle. while the pressure in the left auricle diminished, and it was suggested that in this way an embolus might pass from the right to the left side of the heart if a pulmonary embolism had occurred a short time previously.

4. Dr. J. W. McNEE on *The Clinical and Pathological Classification of Chronic Splenomegaly in Britain*. At the meeting of the Association at Belfast in 1927, some preliminary work on the comparative anatomy of the spleen was described which had a direct bearing on the problems of splenomegaly. Before and since then nearly two hundred spleens had been examined, and a tentative classification on a histological basis has been based on the observations. No clinical classification of any adequate kind was yet possible, but might follow later by correlation of pathological findings with clinical signs and symptoms. The term ' Banti's disease' should practically disappear from British literature, being retained only for the rare type of splenomegaly which Banti described. Splenic anaemia is the most convenient and suitable clinical description for the present. A table showing a tentative classification of the chronic forms of splenomegaly was presented.

Drs. Lewis Smith, Cowan, Gibson, L. Findlay, and others discussed the communication.

5. Dr. F. J. NATTRASS described the results obtained in a series of cases of *Sub-acute Combined Degeneration of the Cord treated by Liver-feeding*. Of 61 cases, 30 received liver treatment. Consistently good results were obtained in the early cases, and marked improvement, especially in regard to ataxia, in most of the established cases. Advanced cases, especially if complicated by sepsis, might fail to respond at all. More prolonged treatment is necessary to obtain improvement in the nervous symptoms than for the cure of the anaemia.

Sir J. Purves-Stewart denied that degeneration can be cured, and ascribed the above cases to the toxic stage in the central nervous system.

Dr. Cohen had seen degeneration develop while under liver treatment.

Dr. Bramwell ascribed the improvement to re-education.

Lord Dawson and Dr. Eason also discussed the communication.

Dr. GEORGE RIDDOCH described two cases, one cystic and the other non-cystic, of *Haemangiomata in the Region of the Fourth Ventricle.* He discussed the symptomatology and differential diagnosis of these tumours. He laid stress on the age of the patient when symptoms first appear, the prominence of intermittent hydrocephalus in the early part of the course, and the frequent paucity of cerebellar signs and symptoms apart from giddiness and a stiff attitude of the head, even when the illness is advanced. Nystagmus and hypotonia may for long be absent. Amongst extra-cerebellar signs, angioma of the retina, which Lindau has shown to be occasionally present, as well as angiomata elsewhere, and defective postural sensibility in the limbs, with astereognosis, are the most interesting.

The Annual Dinner was held in St. John's College at 8 p.m. The President, Sir Humphry Rolleston, was in the Chair. The Official Guests included the Mayor of Cambridge, Professor Barcroft, and Mr. L. E. Shore. One hundred and fifty-nine members and guests were present.

Saturday Morning Session.

1. Dr. J. CRIGHTON BRAMWELL on *Some Graphic Records of Heart Murmurs.* He described a simple optical method of recording heart sounds and murmurs. He referred to the value of graphic records for determining the exact time relations of different murmurs, and showed records taken from a case of mitral stenosis with partial heart-block, illustrating the relation of the crescendo murmur to auricular systole.

2. Dr. CHANDLER gave a communication on *Therapeutic Oleothorax.* Therapeutic oleothorax is employed usually as an adjunct to artificial pneumothorax treatment. Some of its more important uses are: (1) To prevent the unwanted expansion of the lung by obliterative pleurisy in the course of artificial pneumothorax treatment. (2) To act as a more constant pressure collapse medium. (3) Possibly as a more permanent collapse medium. (4) In certain cases of tuberculous empyema. (5) In a case of small persistent broncho-pleural fistulae after spontaneous pneumothorax. The oil used is sterile olive oil, in which is incorporated oil of gomenol in a strength of 5 per cent. The technique of injection was described, and lantern slides of illustrative cases were shown.

The communication was discussed by Drs. Morley Fletcher and L. Findlay.

3. Dr. J. PARKINSON and Dr. D. EVAN BEDFORD on *The Advantages of Radioscopy over Percussion of the Heart.* The limited value of percussion was emphasized. Radioscopy is more accurate and gives information not only as to size, of value in prognosis, but as to shape, of special value in diagnosis. Visualization of each auricle also gives new information. Lantern slides were shown to illustrate diseases of the pulmonary artery, non-syphilitic diseases of the aorta, and affections of the right and left auricles.

Drs. Poulton, Stacey Wilson, Abrahams, Claude Wilson, and Wilkinson discussed this communication.

4. Dr. A. F. HURST discussed *The Precursors of Carcinoma of the Stomach.* Whereas about 20 per cent. of cases of carcinoma of the stomach are secondary to chronic gastric ulcer, most of the remaining 80 per cent. are secondary to chronic gastritis. No cases have been recorded in which progressive diminution in the quantity of free hydrochloric acid has been observed during the development of cancer, and it is probable that when achlorhydria is present, it is due to chronic

gastritis, which precedes the development of the carcinoma, and not to the carcinoma itself. Thus all but one of 10 cases of carcinoma ventriculi with a history of eighteen months or more had free acid, whereas 16 out of 18 with less than six months' history had achlorhydria. Many other facts point strongly to the conclusion that achlorhydria is not a late stage of the condition in which free acid is present, but is already present as a result of gastritis when the growth develops. In both gastritis and carcinoma free acid often appears after lavage, and the total chloride is increased in contrast with the low figures found in the true achylia gastrica. This would explain the cases of cancer of the stomach associated with Addison's anaemia and sub-acute combined degeneration of the cord, the symptoms of which precede those of the stomach disease, the achlorhydria which predisposes to their development being present before there is a growth. Thus we may hope to provide a real prophylaxis of carcinoma ventriculi by early diagnosis and efficient medical treatment of gastric ulcer, and by the recognition that chronic gastritis with achlorhydria is a very common condition, which can be successfully treated by lavage with hydrogen peroxide in addition to dealing with its exciting causes.

Sir William Willcox advised the estimation of active hydrochloric acid as opposed to free hydrochloric acid.

Dr. Hurst replied.

5. Sir WILLIAM WILLCOX gave an important communication on *Some Cases of Cirrhosis of the Liver due to Toxic Agents other than Alcohol.* Reference was made to cases presenting the clinical symptoms and pathological characters of cirrhosis of the liver, the cause being some chemical toxic agent other than alcohol. Cirrhosis of the liver may result from the hepatitis arising from toxins of bacterial or protozoal origin—for example, from syphilis, malaria, kala-azar, amoebic dysentery, bilharzia, &c. Examples of chemical liver poisons were compounds of arsenic both organic and inorganic, phosphorus, chloroform, tetrachlorethane, carbon tetrachloride, trinitrotoluene, dinitrobenzene, dinitrophenol, toluylene-diamine, phenylhydrazine. Quinoline derivatives, such as atophan, atophenyl, and atoquinol, and numerous other examples, might be quoted. Acute yellow atrophy and toxic jaundice are degrees in severity. Inorganic arsenic compounds may cause toxic jaundice or cirrhosis of the liver. A case of cirrhosis of the liver from arsenobenzol was described. Two cases of cirrhosis of the liver with ascites following on the toxic jaundice resulting from prolonged exposure to tetrachlorethane vapour were referred to. A case of typical cirrhosis of the liver was described which occurred in a patient who became the subject of addiction to inhalation of chloroform vapour. The clinical symptoms were characteristic, ascites developed and the patient died from typical symptoms of cirrhosis of the liver. Two cases of cirrhosis of the liver were described which occurred in non-alcoholics who had suffered from toxic jaundice due to trinitrotoluene many years previously. Quinoline derivatives, such as atophan, atophenyl, atoquinol, have been well known to give rise to toxic jaundice. There seems little doubt that these substances may give rise to cirrhosis of the liver in prolonged use. The conclusion arrived at was that any chemical toxic agents which act on the liver, causing toxic jaundice, may under certain conditions give rise to a fibrosis of the liver resulting in the clinical and pathological condition of cirrhosis of the liver.

Many members joined in the discussion, including Dr. Langdon Brown, who referred to the effects of atophan.

Sir William Willcox replied.

6. Dr. J. M. H. CAMPBELL on *The Causes of Paroxysmal Auricular Fibrillation.* Of 160 cases of paroxysmal auricular fibrillation there were in about half typical recurrent attacks, and in the remainder various types from single short attacks to long periods of fibrillation apparently established, but terminating spontaneously. The aetiological factor was hypertension or some arteriosclerotic change in about 45 per cent., and rheumatism in about 25 per cent., i. e. there was probably structural heart disease in 70 per cent. Of the remainder, disorders of the thyroid were responsible for 15 per cent., and in the last 15 per cent. the heart was apparently

healthy. Toxic factors, e. g. sepsis, tobacco, a gastro-intestinal disturbance, seemed important in about half of these last, but no cause at all could be suggested for the other half of this last group.

Dr. J. Hay believed that physical effort may be a cause.

Dr. A. E. Russell considered that infection as from tonsils may be the cause in some cases recorded as hypertension.

Sir William Willcox and Dr. Starling suggested aural suppuration as a cause.

Drs. Ritchie, Phear, and Kauffman joined in the discussion.

Dr. Campbell replied.

2–3 p.m.

Exhibition of the Harvey Film, followed by Film by Professor W. E. Dixon on *Brownian Movement.*

3 p.m. *Afternoon Session.*

1. Dr. A. P. THOMSON described *A Case of Psittacosis.* A woman of 55 developed an insidious illness, characterized in the early stages by fever, headache, prostration, anorexia, and vomiting. She subsequently became delirious, and was found to have a few râles at the left apex. At this stage the blood gave a positive Widal, and a diagnosis of typhoid infection was made. During the third week of the fever it was discovered accidentally that she had been in contact with a sick parrot for some time before her illness began, and eventually *B. psittacosis* was recovered in pure culture from the patient.

Several members discussed this communication.

2. Dr. J. F. GASKELL showed *A Nine-months' Chart in Acute Rheumatoid Arthritis* in a patient aged 30, starting two months after the onset, which was fairly acute. The chart showed a slight daily rise of temperature, never above 100° F., for seven months, and also a slight extra rise lasting six to seven days with the involvement of each new joint. Treatment by massage only for nearly a year resulted in almost complete restitution of all joints to a normal condition.

3. Dr. J. C. SPENCE, under the title of *Glycosuria and Hypoglycaemia following Gastro-enterostomy,* described some studies he had made showing that glycosuria was a frequent sequel of gastro-enterostomy; that it was of the alimentary type with a so-called 'lag' blood-sugar curve; and that it did not lead to true diabetes. He held that these facts were of importance mainly for the light they threw on the 'lag' type of blood-sugar curve. Automatic reactionary hypoglycaemia followed in some of the cases, and he described some experimental work on some of these, showing the conditions under which this phenomenon was likely to occur.

This communication was discussed by Drs. Graham, Hutchison, Poulton, Leyton, Langdon Brown, and other members.

4. Dr. FF. ROBERTS (introduced) on *A Condition simulating and probably preceding Duodenal Ulcer.* The association of gastric hypersecretion with duodenal ulcer is well known. The general view is that the hypersecretion is a reflex effect of the ulcer, like the hypersecretion due to chronic appendicitis. A considerable proportion of gastric cases referred for X-ray examination have the following characteristics : a long history of epigastric pain $1\frac{1}{2}$ to 2 hours after food, relieved by food; vomiting is absent. The duodenal cap shows no ulcer, but may be slightly tender to palpation. The most striking feature is the presence of gastric juice in considerable excess. These cases yield readily to medical treatment and dieting. It seems highly probable that, if left untreated, ulcer would develop.

Drs. A. F. Hurst and R. Hutchison discussed this communication.

5. Dr. NOAH MORRIS on *Observations on the Metabolism and Blood Chemistry in Congenital Hypertrophic Pyloric Stenosis.* In congenital pyloric stenosis the breathing is slow and shallow (Biot type). There is alkalaemia with reduction in the chloride content, and increase in the total CO_2 and non-protein nitrogen of the blood. There is marked correlation between the value for the CO_2 content and the respiratory rate, and also between the former value and the change in weight. Excessive vomiting in infants is not a cause of alkalosis in conditions other than pyloric stenosis or similar obstructive condition. Particulars were given of a case of pyloric stenosis without vomiting, but with all the clinical and biochemical findings of an alkalosis. The construction of a theoretical CO_2 dissociation curve revealed the presence of an excessive amount of available base and a low normal buffering value.

This communication was discussed by Drs. L. G. Parsons, Imrie, Gillespie, and others.